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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).			
(72) Inventors: ADEMA, Gosse, Jan; Haydnstraat 53, NL-6561 ED Groesbeek (NL). MEYAARD, Linde; Realengracht 68, NL-1013 KW Amsterdam (NL). GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US). MCCLANAHAN, Terrill, K.; 1081 Winchester Drive, Sunnyvale, CA 94087 (US). ZURAWSKI, Sandra, M.; 2005 School Road, San Juan Bautista, CA 95045 (US). ZURAWSKI, Gerard; 2005 School Road, San Juan Bautista, CA 95045 (US). LANIER, Lewis, L.; 1528 Frontero Avenue, Los Altos, CA 94024 (US). PHILLIPS, Joseph, H.; 15 Pine Avenue, San Carlos, CA 94070 (US).		Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: ISOLATED MAMMALIAN MONOCYTE CELL GENES; RELATED REAGENTS			
(57) Abstract Nucleic acids encoding various monocyte cell proteins from a primate, reagents related thereto, including specific antibodies, and purified proteins are described. Methods of using said reagents and related diagnostic kits are also provided.			

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ISOLATED MAMMALIAN MONOCYTE CELL GENES; RELATED REAGENTS

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This filing claims benefit of priority to provisional U.S. Patent Applications USSN 60/032,252, filed December 6, 1996; USSN 08/762,187, filed December 9, 1996; USSN 60/033,181, filed December 16, 1996; and USSN 60/041,279, filed March 21, 1997, each of which is incorporated

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herein by reference.

FIELD OF THE INVENTION

The present invention contemplates compositions related to genes found in monocyte cells, cells which function in the immune system. These genes function in controlling development, differentiation, and/or physiology of the mammalian immune system. In particular, the application provides nucleic acids, proteins, antibodies, and methods of using them.

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BACKGROUND OF THE INVENTION

The circulating component of the mammalian circulatory system comprises various cell types, including red and white blood cells of the erythroid and myeloid cell lineages. See, e.g., Rapaport (1987) Introduction to Hematology (2d ed.) Lippincott, Philadelphia, PA; Jandl (1987) Blood: Textbook of Hematology, Little, Brown and Co., Boston, MA.; and Paul (ed.) (1993) Fundamental Immunology (3d ed.) Raven Press, N.Y.

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Monocytes are phagocytic cells that belong to the mononuclear phagocyte system and reside in the circulation. See Roitt (ed) Encyclopedia of Immunology Academic Press, San Diego. These cells originate in the bone marrow and remain only a short time in the marrow compartment once they differentiate. They then enter the circulation and can remain there for a relatively long period of time, e.g., a few days. The monocytes can enter the tissues and body cavities by the process designated diapedesis, where they differentiate into macrophages and possibly into dendritic cells. In an inflammatory response, the number of monocytes in the circulation may double, and many of the increased number of monocytes diapedese to the site of inflammation.

Antigen presentation refers to the cellular events in which a proteinaceous antigen is taken up, processed by antigen presenting cells (APC), and then recognized to initiate an immune response. The most active antigen presenting cells have been characterized as the macrophages, which are direct developmental products from monocytes; dendritic cells; and certain B cells.

Macrophages are found in most tissues and are highly active in internalization of a wide variety of protein antigens and microorganisms. They have a highly developed endocytic activity, and secrete many products important in the initiation of an immune response. For this reason, it is believed that many genes expressed by monocytes or induced by monocyte activation are likely to be important in antigen uptake, processing, presentation, or regulation of the resulting immune response.

However, monocytes are poorly characterized, both in terms of proteins they express, and many of their functions and mechanisms of action, including their activated states. In particular, the processes and mechanisms related to the initiation of an immune response, including antigen processing and presentation, remain unclear. The absence of knowledge about the structural, biological, and physiological properties of these cells limits their understanding. Thus, medical conditions where regulation, development, or physiology of antigen presenting cells is unusual remain unmanageable.

SUMMARY OF THE INVENTION

The present invention is based, in part, upon the discovery of various genes isolated from activated monocytes. These molecules have been designated FDF03 (a type I transmembrane protein with Ig-like extracellular portion); YE01 (an Fc gamma/alpha-like receptor); and KTE03 class (cell surface receptors exhibiting Ig-like domains), represented by YYB01 and YYB04 related embodiments.

The invention provides various compositions of matter selected from: a substantially pure or recombinant FDF03 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 2 or 4; a natural sequence FDF03 of SEQ ID NO: 2 or 4; a fusion protein comprising FDF03 sequence; a substantially pure or recombinant YE01 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 6, 8, or 10; a natural sequence YE01 of SEQ ID

NO: 6, 8, or 10; a fusion protein comprising YE01 sequence; a substantially pure or recombinant KTE03 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 12, 14, or 16; a natural sequence KTE03 of
5 SEQ ID NO: 12, 14, 16, 18, 20 or 22; or a fusion protein comprising KTE03 sequence. Preferably, the substantially pure or isolated protein comprises a segment exhibiting sequence identity to a corresponding portion of a FDF03, YE01, or KTE03, wherein: the homology is at least about 90% identity and the portion is at least about 9 amino acids; the
10 homology is at least about 80% identity and the portion is at least about 17 amino acids; or the homology is at least about 70% identity and the portion is at least about 25 amino acids. In other forms, the invention provides such composition of matter, wherein the: FDF03 comprises a mature sequence of SEQ ID NO: 2 or 4; YE01 comprises a mature
15 sequence of SEQ ID NO: 6, 8, or 10; KTE03 comprises a mature sequence of SEQ ID NO: 12, 14, 16, 18, 20 or 22; or the protein or peptide: is from a warm blooded animal selected from a mammal, including a primate or rodent; comprises at least one polypeptide segment of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22; exhibits a plurality of portions exhibiting the
20 identity; is a natural allelic variant of FDF03, YE01, or KTE03; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a mammalian FDF03, YE01, or KTE03; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a rodent FDF03, YE01, or KTE03; exhibits
25 at least two non-overlapping epitopes which are specific for a primate FDF03, YE01, or KTE03; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a primate FDF03, YE01, or KTE03; is glycosylated; has a molecular weight of at least 7 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid
30 substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Other compositions include those comprising: a sterile FDF03 protein or peptide; the FDF03 protein or peptide and a carrier, wherein
35 the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile YE01 protein or peptide; the YE01 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal,

nasal, topical, or parenteral administration; a sterile KTE03 protein or peptide; or the KTE03 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

In fusion protein embodiments, the invention provides those which comprise: mature protein sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another cell surface protein.

Various kits include those comprising a protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Antibodies and binding compounds include those comprising an antigen binding portion from an antibody, which specifically binds to a natural FDF03, YE01, or KTE03 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22; is raised against a mature FDF03, YE01, or KTE03; is raised to a purified FDF03, YE01, or KTE03; is immunoselected; is a polyclonal antibody; binds to a denatured FDF03, YE01, or KTE03; exhibits a Kd to antigen of at least 30 mM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. A kit comprising the binding compound is provided including, e.g., the binding compound and: a compartment comprising the binding compound; and/or instructions for use or disposal of reagents in the kit. Preferably, the kit is capable of making a qualitative or quantitative analysis.

Various other compositions include those comprising: a sterile binding compound; or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a protein or peptide or fusion protein as described, wherein: the protein is from a mammal, including a primate; or the nucleic acid: encodes an antigenic peptide sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22; encodes a plurality of antigenic peptide

sequences of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22; exhibits at least about 80% identity to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic
5 nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the protein; or is a PCR primer, PCR product, or mutagenesis primer.

Various cells are provided, including those comprising a
10 described recombinant nucleic acid. Preferably, the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Kits with such nucleic acids include those with the nucleic acid and: a compartment comprising the nucleic acid; a compartment further
15 comprising a FDF03, YE01, or KTE03 protein or polypeptide; and/or instructions for use or disposal of reagents in the kit. Preferably, the kit is capable of making a qualitative or quantitative analysis.

Other nucleic acids include those which: hybridize under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 1 or 3; hybridize
20 under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 5, 7, or 9; hybridize under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 11, 13, 15, 17, 19 and 21; exhibit at least about 85% identity over a stretch of at least about 30 nucleotides to a primate FDF03; exhibit at least about 85% identity over a stretch of at least about 30 nucleotides
25 to a primate YE01; or exhibit at least about 85% identity over a stretch of at least about 30 nucleotides to a primate KTE03. In preferred embodiments, the wash conditions are at 45° C and/or 500 mM salt; or at 55° C and/or 150 mM salt; or the identity is at least 90% and/or the stretch is at least 55 nucleotides; or the identity is at least 95% and/or the
30 stretch is at least 75 nucleotides.

The invention further provides a method of modulating physiology or development of a cell or tissue culture cell comprising contacting the cell with an agonist or antagonist of a FDF03, YE01, or KTE03. In preferred embodiments, the cell is a leukocyte, and the
35 antagonist is to YE01 and is a monoclonal antibody which binds to DLAIR-1.

DETAILED DESCRIPTION

I. General

The present invention provides DNA sequences encoding mammalian proteins expressed on monocytes. For a review of monocytes and their functions, see, e.g., Gallin, et al. (eds. 1988) Inflammation: Basic Principles and Clinical Correlates Raven Press, NY; van Furth (ed. 1985) Mononuclear Phagocytes: Characteristics, Physiology and Function Martinus Nijhoff, Dordrecht, Netherlands.

Specific human embodiments of these proteins are provided below. The descriptions below are directed, for exemplary purposes, to human monocyte genes, but are likewise applicable to structurally, e.g., sequence, related embodiments from other sources or mammalian species, including polymorphic or individual variants. These will include, e.g., proteins which exhibit a relatively few changes in sequence, e.g., less than about 5%, and number, e.g., less than 20 residue substitutions, typically less than 15, preferably less than 10, and more preferably less than 5 substitutions. These will also include versions which are truncated from full length, as described, and fusion proteins containing substantial segments of these sequences.

II. Definitions

The term "binding composition" refers to molecules that bind with specificity to a these monocyte proteins, e.g., in an antibody-antigen interaction, or compounds, e.g., proteins, which specifically associate with the respective protein. Typically, the association will be in a natural physiologically relevant protein-protein interaction, either covalent or non-covalent, and may include members of a multiprotein complex, including carrier compounds or dimerization partners. The molecule may be a polymer, or chemical reagent. A functional analog may be a protein with structural modifications, or may be a wholly unrelated molecule, e.g., which has a molecular shape which interacts with the appropriate interacting determinants. The variants may serve as agonists or antagonists of the protein, see, e.g., Goodman, et al. (eds.) (1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press, Tarrytown, N.Y.

The term "binding agent:monocyte protein complex", as used herein, refers to a complex of a binding agent and the monocyte protein. Specific binding of the binding agent means that the binding agent has a specific binding site that recognizes a site on the respective monocyte

protein. For example, antibodies raised to the monocyte protein and recognizing an epitope on the monocyte protein are capable of forming a binding agent:monocyte protein complex by specific binding.

Typically, the formation of a binding agent:monocyte protein complex allows the measurement of monocyte protein in a mixture of other proteins and biologics. The term "antibody:monocyte protein complex" refers to a binding agent:monocyte protein complex in which the binding agent is an antibody. The antibody may be monoclonal, polyclonal or even an antigen binding fragment of an antibody.

"Homologous" nucleic acid sequences, when compared, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison and/or phylogenetic relationship, or based upon hybridization conditions. Hybridization conditions are described in greater detail below.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially separated from other components which naturally accompany a native sequence, e.g., proteins and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule. An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain minor heterogeneity. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

As used herein, the term "monocyte protein" shall encompass, when used in a protein context, a protein having amino acid sequences as shown in SEQ ID NO: 2 or 4; 6, 8, or 10; or 12, 14, or 16, or a significant fragment of such a protein. It refers to a polypeptide which interacts with the respective monocyte protein specific binding components. These binding components, e.g., antibodies, typically bind to the monocyte protein with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM.

The term "polypeptide" or "protein" as used herein includes a significant fragment or segment of said monocyte protein, and

encompasses a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Fragment or size limitations applicable for comparison to one group, e.g., to the FDF03, do not necessarily imply similar size limitations on fragments for the others.

A "recombinant" nucleic acid is defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants. Thus, for example, products made by transforming cells with any non-naturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode polypeptides similar to fragments of these antigens, and fusions of sequences from various different species variants.

"Solubility" is reflected by sedimentation measured in Svedberg units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation velocity was classically performed in an analytical ultracentrifuge, but is

typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d ed.) W.H. Freeman & Co., San Francisco, CA; and Cantor and Schimmel (1980) Biophysical Chemistry parts 1-3, W.H. Freeman & Co., San Francisco, CA. As a crude
5 determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually
10 less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less than about 3S. Solubility of a polypeptide or fragment depends upon the environment and the polypeptide. Many parameters affect polypeptide solubility, including temperature, electrolyte environment, size and molecular
15 characteristics of the polypeptide, and nature of the solvent. Typically, the temperature at which the polypeptide is used ranges from about 4° C to about 65° C. Usually the temperature at use is greater than about 18° C and more usually greater than about 22° C. For diagnostic purposes, the temperature will usually be about room temperature or
20 warmer, but less than the denaturation temperature of components in the assay. For therapeutic purposes, the temperature will usually be body temperature, typically about 37° C for humans, though under certain situations the temperature may be raised or lowered in situ or in vitro.

25 The size and structure of the polypeptide should generally be in a substantially stable state, and usually not in a denatured state. The polypeptide may be associated with other polypeptides in a quaternary structure, e.g., to confer solubility, or associated with lipids or detergents in a manner which approximates natural lipid bilayer interactions.

30 The solvent will usually be a biologically compatible buffer, of a type used for preservation of biological activities, and will usually approximate a physiological solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, a detergent will be added, typically a mild non-
35 denaturing one, e.g., CHS or CHAPS, or a low enough concentration as to avoid significant disruption of structural or physiological properties of the protein.

"Substantially pure" typically means that the protein is isolated from other contaminating proteins, nucleic acids, and other biologicals

derived from the original source organism. Purity, or "isolation" may be assayed by standard methods, and will ordinarily be at least about 50% pure, more ordinarily at least about 60% pure, generally at least about 70% pure, more generally at least about 80% pure, often at least about 85% pure, more often at least about 90% pure, preferably at least about 95% pure, more preferably at least about 98% pure, and in most preferred embodiments, at least 99% pure.

"Substantial similarity" in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least 56%, more generally at least 59%, ordinarily at least 62%, more ordinarily at least 65%, often at least 68%, more often at least 71%, typically at least 74%, more typically at least 77%, usually at least 80%, more usually at least about 85%, preferably at least about 90%, more preferably at least about 95 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides. Alternatively, substantial similarity exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence derived from SEQ ID NO: 1 or 3; 5, 7, or 9; or 11, 13, or 15. Typically, selective hybridization will occur when there is at least about 55% similarity over a stretch of at least about 30 nucleotides, preferably at least about 65% over a stretch of at least about 25 nucleotides, more preferably at least about 75%, and most preferably at least about 90% over about 20 nucleotides. See, e.g., Kanehisa (1984) Nuc. Acids Res. 12:203-213. The length of similarity comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides.

"Stringent conditions", in referring to homology or substantial similarity in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. The combination of parameters is more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370. A nucleic acid probe which binds to a target nucleic acid under

stringent conditions is specific for said target nucleic acid. Such a probe is typically more than 11 nucleotides in length, and is sufficiently identical or complementary to a target nucleic acid over the region specified by the sequence of the probe to bind the target under stringent hybridization conditions.

Counterpart monocyte proteins from other mammalian species can be cloned and isolated by cross-species hybridization of closely related species. See, e.g., below. Similarity may be relatively low between distantly related species, and thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody preparation which exhibits less species specificity may be useful in expression cloning approaches.

The phrase "specifically binds to an antibody" or "specifically immunoreactive with", when referring to a protein or peptide, refers to a binding reaction which is determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biological components. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein and do not significantly bind other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity for a particular protein. For example, antibodies raised to the human monocyte protein immunogen with the amino acid sequence depicted in SEQ ID NO: 2 can be selected to obtain antibodies specifically immunoreactive with that monocyte protein and not with other proteins. These antibodies recognize proteins highly similar to the homologous human monocyte protein.

III. Nucleic Acids

These monocyte genes are specifically expressed on dendritic cells. The preferred embodiments, as disclosed, will be useful in standard procedures to isolate genes from other species, e.g., warm blooded animals, such as birds and mammals. Cross hybridization will allow isolation of related proteins from individuals, strains, or species. A number of different approaches are available successfully to isolate a suitable nucleic acid clone based upon the information provided herein. Southern blot hybridization studies should identify homologous genes in other species under appropriate hybridization conditions.

Purified protein or defined peptides are useful for generating antibodies by standard methods, as described below. Synthetic peptides

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or purified protein can be presented to an immune system to generate polyclonal and monoclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press, NY, which are incorporated herein by reference. Alternatively, a CD protein binding composition can be useful as a specific binding reagent, and advantage can be taken of its specificity of binding, for, e.g., purification of a monocyte protein.

The specific binding composition can be used for screening an expression library made from a cell line which expresses the respective monocyte protein. Many methods for screening are available, e.g., standard staining of surface expressed ligand, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells expressing the ligand.

The peptide segments can also be used to produce appropriate oligonucleotides to screen a library to determine the presence of a similar gene, e.g., an identical or polymorphic variant, or to identify a monocyte. The genetic code can be used to select appropriate oligonucleotides useful as probes for screening. In combination with polymerase chain reaction (PCR) techniques, synthetic oligonucleotides will be useful in selecting desired clones from a library.

Complementary sequences will also be used as probes or primers. Based upon identification of the likely amino terminus, other peptides should be particularly useful, e.g., coupled with anchored vector or poly-A complementary PCR techniques or with complementary DNA of other peptides.

Techniques for nucleic acid manipulation of genes encoding these monocyte proteins, e.g., subcloning nucleic acid sequences encoding polypeptides into expression vectors, labeling probes, DNA hybridization, and the like are described generally in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2nd ed.) Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, which is incorporated herein by reference and hereinafter referred to as "Sambrook, et al." See also, Coligan, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology Greene/Wiley, New York, NY, referred to as "Coligan, et al."

There are various methods of isolating the DNA sequences encoding these monocyte proteins. For example, DNA is isolated from a

genomic or cDNA library using labeled oligonucleotide probes having sequences identical or complementary to the sequences disclosed herein. Full-length probes may be used, or oligonucleotide probes may be generated by comparison of the sequences disclosed with other proteins and selecting specific primers. Such probes can be used directly in hybridization assays to isolate DNA encoding monocyte proteins, or probes can be designed for use in amplification techniques such as PCR, for the isolation of DNA encoding monocyte proteins.

To prepare a cDNA library, mRNA is isolated from cells which express the monocyte protein. cDNA is prepared from the mRNA and ligated into a recombinant vector. The vector is transfected into a recombinant host for propagation, screening and cloning. Methods for making and screening cDNA libraries are well known. See Gubler and Hoffman (1983) Gene 25:263-269; Sambrook, et al.; or Coligan, et al.

For a genomic library, the DNA can be extracted from tissue and either mechanically sheared or enzymatically digested to yield fragments of about 12-20 kb. The fragments are then separated by gradient centrifugation and cloned in bacteriophage lambda vectors. These vectors and phage are packaged in vitro, as described, e.g., in Sambrook, et al. or Coligan, et al. Recombinant phage are analyzed by plaque hybridization as described in Benton and Davis (1977) Science 196:180-182. Colony hybridization is carried out as generally described in, e.g., Grunstein, et al. (1975) Proc. Natl. Acad. Sci. USA 72:3961-3965.

DNA encoding a monocyte protein can be identified in either cDNA or genomic libraries by its ability to hybridize with the nucleic acid probes described herein, for example in colony or plaque hybridization experiments. The corresponding DNA regions are isolated by standard methods familiar to those of skill in the art. See Sambrook, et al.

Various methods of amplifying target sequences, such as the polymerase chain reaction, can also be used to prepare DNA encoding monocyte proteins. Polymerase chain reaction (PCR) technology is used to amplify such nucleic acid sequences directly from mRNA, from cDNA, and from genomic libraries or cDNA libraries. The isolated sequences encoding monocyte proteins may also be used as templates for PCR amplification.

In PCR techniques, oligonucleotide primers complementary to two 5' regions in the DNA region to be amplified are synthesized. The polymerase chain reaction is then carried out using the two primers.

See Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA. Primers can be selected to amplify the entire regions encoding a selected full-length monocyte protein or to amplify smaller DNA segments as desired. Once such regions are PCR-amplified, they can be sequenced and oligonucleotide probes can be prepared from sequence obtained using standard techniques. These probes can then be used to isolate DNAs encoding other forms of the monocyte proteins.

Oligonucleotides for use as probes are chemically synthesized according to the solid phase phosphoramidite triester method first described by Beaucage and Carruthers (1983) Tetrahedron Lett. 22(20):1859-1862, or using an automated synthesizer, as described in Needham-VanDevanter, et al. (1984) Nucleic Acids Res. 12:6159-6168. Purification of oligonucleotides is performed e.g., by native acrylamide gel electrophoresis or by anion-exchange HPLC as described in Pearson and Regnier (1983) J. Chrom. 255:137-149. The sequence of the synthetic oligonucleotide can be verified using the chemical degradation method of Maxam and Gilbert in Grossman and Moldave (eds.) (1980) Methods in Enzymology 65:499-560 Academic Press, New York.

A nucleic acid has been isolated which encodes a human protein which is a type I transmembrane protein comprising an extracellular portion characterized by Ig-like domains, indicating that this gene encodes a receptor member of the Ig superfamily. This 1249 bp clone was isolated from a monocyte cell library and has been designated FDF03. Its nucleotide sequence and corresponding open reading frame are provided in SEQ ID NO: 1 and 2, respectively. The putative coding region runs from about 154 to 1062. An N-terminal hydrophobic sequence, e.g., a putative signal sequence, corresponds to about amino acid residues -19(met) to -1(leu), and a internal hydrophobic segment, corresponding to a putative transmembrane segment runs from around ala177 to leu199. The extracellular region is probably about 170 amino acids, with a potential Ig-like domain structure; the intracellular region is about 80 residues. Sequence analysis indicates similarity to GenBank clones H26010 and R50327 from humans.

Other mammalian counterparts should become available. For example, a partial rodent gene is described in SEQ ID NO: 3 and 4. A partial human/mouse alignment is provided in Table 1. Standard techniques will allow isolation of other counterparts, or to extend partial sequences.

Table 1 Partial alignment of human/mouse FDF03 protein.

```

5      hu
      MGRPLLLP LLLP LLLP PAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE
      mo  MAQVLLLLSSGCLHAGNSERYNRKNG-----
      FGVNQPERCSGVQGGSIDIPFSFYFPWK

10     hu
      LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQK...
      mo  LAKDPQMSIAWKWKDFHGEVIYNSSLPFIHEHFKGRLILNWTQGG...

```

15 A second human monocyte cell clone was isolated from an activated monocyte cell library and is designated YE01. YE01 is related to the receptors for Fc gamma and/or Fc alpha. This protein is referred to herein as an Fc gamma/alpha receptor and is described in SEQ ID NO: 5 and 6. A mouse counterpart is probably encoded in the EST W55567.

20 A similar gene was cloned by expressing cloning using a monoclonal antibody DX26, which was raised against the immunogen of human NK cell clone NK681.D5, and selected for inhibiting killing by NK cell clones of Fc receptor bearing target cells (SP2/0). This isolate is described in SEQ ID NO: 7 and 8.

25 Nucleic acid and putative amino acid sequence of a soluble form of the receptors, termed DLAIR-2, is disclosed in SEQ ID NO: 9 and 10. The signal sequence runs from about Met1 to Thr21. While the gene was initially described as a monocyte derived gene, expression analysis indicates that it is more specific for expression on lymphocytes. Thus, in the case of YE01, the descriptor "monocyte gene" may indicate its original identification in a population enriched for that cell type, though

30 it may have also contained some other cell types. Sequence analysis suggests YE01 is a member of the Ig superfamily of receptors, and is closely related to the CD8 family, which contain a V1J-type fold, particularly the Fc receptors alpha and/or gamma. Because it contains an ITAM-like motif, the protein may well be a lymphocyte version of

35 the Killer Inhibitory Receptors (KIR), which send a negative signal to inhibit killer cell function. This protein exhibits similar function in inhibiting lymphocyte effector function, e.g., antigen presentation or subsequent response initiation.

40 In particular, signaling through the molecule recognized by DX26 mAb (designated DNAX Leukocyte Associated Immunoglobulin-like Receptor (DLAIR)), delivers a negative signal to NK cell clones that prevents their killing specific target cells. However, the molecule is expressed on other lymphocytes, including T cells and monocytes.

Thus, the DX26 antibody probably represents an antibody which both inhibits NK and cytotoxic T cell killing, and the monocyte distribution suggests that the molecule may inhibit monocyte-mediated or lymphocyte-mediated effector functions.

5 A third monocyte gene was isolated and designated KTE03, and is represented by six related embodiments, designated YYB01, YYB04 (forms 1 and 2), KLM63, KLM66, and KLM67. Note that a possible splice variant, which may encode a variant protein form, has also been detected.

10 SEQ ID NO: 11-22 provide human KTE03 sequences, e.g., alternative splicing, encoding related proteins with homology to several NK KIR surface molecules, and to the Fc receptors gamma and alpha. The YYB01 coding sequence appears to run from about 81 to 1397. The message appears to be IL-10 upregulated. See SEQ ID NO: 11
15 and 12. Because of significant identity of sequence which ends at specific locations, it appears that there may be splice junctions around nucleotide 36, 1264, and 1587. The YYB04 sequence provided indicates that certain insertions of sequence lead to a frameshift and alternative carboxy terminal sequence. Moreover, certain peculiar
20 differences in sequence suggest either sequencing errors, or a mechanism of variability generated by a mechanism perhaps analogous to hypervariable region combinations.

SEQ ID NO: 13 and 14 set forth the nucleic acid and amino
25 acid sequences of YYB04, which is related to YYB01, apparently through alternative splicing from the same or a very highly related gene. The coding region runs from about 191 to 1493, but the initiation methionine may actually be at the numbered Met at 18 (see SEQ ID NO: 13 and 14). Another transcript was isolated which contains evidence for existence of an insert of sequence
30 TGCTACGGCT CACTCAACTC CGACCCCTAC CTGCTGTCTC
ACCCAGTGA GCCCCTGGAG CTCGTGGTCT CAGG between
residues 1426 and 1427, which changes the downstream reading
frame of the subsequent sequence, to encode, from residue 413, CYG
35 SLNSD PYLLS HPSEP LELVV SGPSM GSSPP PTGPI STPAG PEDQP
LTPTG SDPQS GLGRH LGVVI GILVA VLLLL LLLLL LFLIL
RHRRQ GKHWT STQRK ADFQH PAGAV GPEPT DRGLQ WRSSP
AADAQ EENLY AAVKD TQPED GVEMD TRAAA SEAPQ DVTYA
QLHSL TLRRK ATEPP PSQER EPPAE PSIYA TLAIH (SEQ ID NO: 15

and 16). This alternative sequence contains a transmembrane segment from about 478 to 500.

A KTE03 embodiment designated KLM63 has also been provided in SEQ ID NO: 17 and 18. Another KTE03 embodiment, designated KLM66, is provided in SEQ ID NO: 19 and 20. Yet another KTE03 embodiment, designated KLM 67, is provided in SEQ ID NO: 21 and 22.

This invention provides isolated DNA or fragments to encode a monocyte protein, as described. In addition, this invention provides isolated or recombinant DNA which encodes a biologically active protein or polypeptide which is capable of hybridizing under appropriate conditions, e.g., high stringency, with the DNA sequences described herein. Said biologically active protein or polypeptide can be a naturally occurring form, or a recombinant protein or fragment, and have an amino acid sequence as disclosed in SEQ ID NO: 2 or 4; 6, 8, or 10; or 12, 14, 16, 18, 20 or 22. Preferred embodiments will be full length natural isolates, e.g., from a primate. In glycosylated form, the proteins should exhibit larger sizes. Further, this invention encompasses the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to each respective monocyte protein. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others.

IV. Making Monocyte Gene Products

DNAs which encode these monocyte proteins or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples.

These DNAs can be expressed in a wide variety of host cells for the synthesis of a full-length protein or fragments which can, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules; and for structure/function studies. Each of these monocyte proteins or their fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially purified to be free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are

particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The antigen, or portions thereof, may be expressed as fusions with other proteins.

5 Expression vectors are typically self-replicating DNA or RNA constructs containing the desired monocytic gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual
10 host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that
15 encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently from the host cell.

The vectors of this invention contain DNAs which encode the
20 various monocytic proteins, or a fragment thereof, typically encoding, e.g., a biologically active polypeptide, or protein. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for a monocytic
25 protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the protein is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells
30 or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized
35 by the host cell. It is also possible to use vectors that cause integration of a monocytic gene or its fragments into the host DNA by recombination, or to integrate a promoter which controls expression of an endogenous gene.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual Elsevier, N.Y.; and Rodriquez, et al. (eds.) (1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses Buttersworth, Boston, MA.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., *E. coli* and *B. subtilis*. Lower eukaryotes include yeasts, e.g., *S. cerevisiae* and *Pichia*, and species of the genus *Dictyostelium*. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, *E. coli* and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or its derivatives. Vectors that can be used to express monocyte proteins or fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez and Denhardt (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses 10:205-236 Buttersworth, Boston, MA.

Lower eukaryotes, e.g., yeasts and *Dictyostelium*, may be transformed with monocyte gene sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, *Saccharomyces cerevisiae*. It will be used generically to represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the desired protein or its fragments, and sequences for

translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are the preferred host cells for expression of the monocytic protein. In principle, most any higher eukaryotic tissue culture cell line may be used, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred to achieve proper processing, both cotranslationally and posttranslationally. Transformation or transfection and propagation of such cells is routine. Useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (e.g., if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also may contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

In certain instances, the monocytic proteins need not be glycosylated to elicit biological responses in certain assays. However, it will often be desirable to express a monocytic polypeptide in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., in unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, a monocytic gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. It is

further understood that over glycosylation may be detrimental to monocyte protein biological activity, and that one of skill may perform routine testing to optimize the degree of glycosylation which confers optimal biological activity.

5 A monocyte protein, or a fragment thereof, may be engineered to be phosphatidyl inositol (PI) linked to a cell membrane, but can be removed from membranes by treatment with a phosphatidyl inositol cleaving enzyme, e.g., phosphatidyl inositol phospholipase-C. This releases the antigen in a biologically active form, and allows purification
10 by standard procedures of protein chemistry. See, e.g., Low (1989) Biochem. Biophys. Acta 988:427-454; Tse, et al. (1985) Science 230:1003-1008; Brunner, et al. (1991) J. Cell Biol. 114:1275-1283; and Coligan, et al. (eds.) (1996 and periodic supplements) Current Protocols in Protein Science, John Wiley & Sons, New York, NY.

15 Now that these monocyte proteins have been characterized, fragments or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis Springer-Verlag, New York, NY; and
20 Bodanszky (1984) The Principles of Peptide Synthesis Springer-Verlag, New York, NY. See also Merrifield (1986) Science 232:341-347; and Dawson, et al. (1994) Science 266:776-779. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride
25 process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes.

30 The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The monocyte proteins of this invention can be obtained in varying degrees of purity depending upon
35 the desired use. Purification can be accomplished by use of known protein purification techniques or by the use of the antibodies or binding partners herein described, e.g., in immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and

contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the proteins as a result of DNA techniques, see below.

5 Multiple cell lines may be screened for one which expresses said protein at a high level compared with other cells. Various cell lines, e.g., a mouse thymic stromal cell line TA4, is screened and selected for its favorable handling properties. Natural monocyte cell proteins can be isolated from natural sources, or by expression from a transformed cell
10 using an appropriate expression vector. Purification of the expressed protein is achieved by standard procedures, or may be combined with engineered means for effective purification at high efficiency from cell lysates or supernatants. FLAG or His₆ segments can be used for such purification features.

15 V. Antibodies

Antibodies can be raised to these various monocyte proteins, including individual, polymorphic, allelic, strain, or species variants, and fragments thereof, both in their naturally occurring (full-length)
20 forms and in their recombinant forms. Additionally, antibodies can be raised to monocyte proteins in either their active forms or in their inactive forms. Anti-idiotypic antibodies may also be used.

a. Antibody Production

A number of immunogens may be used to produce antibodies
25 specifically reactive with these monocyte proteins. Recombinant protein is the preferred immunogen for the production of monoclonal or polyclonal antibodies. Naturally occurring protein may also be used either in pure or impure form. Synthetic peptides made using the human monocyte protein sequences described herein may also be used as
30 an immunogen for the production of antibodies to the monocyte protein. Recombinant protein can be expressed in eukaryotic or prokaryotic cells as described herein, and purified as described. The product is then injected into an animal capable of producing antibodies. Either monoclonal or polyclonal antibodies may be generated for
35 subsequent use in immunoassays to measure the protein.

Methods of producing polyclonal antibodies are known to those of skill in the art. In brief, an immunogen, preferably a purified protein, is mixed with an adjuvant and animals are immunized with the mixture. The animal's immune response to the immunogen

preparation is monitored by taking test bleeds and determining the titer of reactivity to the monocyte protein of interest. When appropriately high titers of antibody to the immunogen are obtained, blood is collected from the animal and antisera are prepared. Further fractionation of the antisera to enrich for antibodies reactive to the protein can be done if desired. See, e.g., Harlow and Lane.

Monoclonal antibodies may be obtained by various techniques familiar to those skilled in the art. Briefly, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell. See, e.g., Kohler and Milstein (1976) Eur. J. Immunol. 6:511-519, which is incorporated herein by reference. Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells according to the general protocol outlined by Huse, et al. (1989) Science 246:1275-1281.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of these monocyte proteins can be raised by immunization of animals with conjugates of the fragments with carrier proteins as described above. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective monocyte proteins, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 100 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better. Standard methods are available for selection of high affinity and selective antibody preparations.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and

Clinical Immunology (4th ed.) Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York, NY; and particularly in Kohler and Milstein (1975) Nature 256:495-497, which discusses one method of generating monoclonal antibodies.

Summarized briefly, this method involves injecting an animal with an immunogen to initiate a humoral immune response. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secretes a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced. See, Cabilly, U.S. Patent No. 4,816,567; and Queen, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033.

The antibodies of this invention can also be used for affinity chromatography in isolating each monocytic protein. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, SEPHADEX, or the like, where a cell lysate may be passed through the column, the column washed, followed by

increasing concentrations of a mild denaturant, whereby purified monocyte protein will be released.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies to monocyte proteins may be used for the analysis or, or identification of specific cell population components which express the respective protein. By assaying the expression products of cells expressing monocyte proteins it is possible to diagnose disease, e.g., immune-compromised conditions, monocyte depleted conditions, or overproduction of monocyte.

Antibodies raised against each monocyte will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

b. Immunoassays

A particular protein can be measured by a variety of immunoassay methods. For a review of immunological and immunoassay procedures in general, see Stites and Terr (eds.) 1991 Basic and Clinical Immunology (7th ed.). Moreover, the immunoassays of the present invention can be performed in any of several configurations, which are reviewed extensively in Maggio (ed.) (1980) Enzyme Immunoassay CRC Press, Boca Raton, Florida; Tijan (1985) "Practice and Theory of Enzyme Immunoassays," Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers B.V., Amsterdam; and Harlow and Lane Antibodies, A Laboratory Manual, supra, each of which is incorporated herein by reference. See also Chan (ed.) (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassays Stockton Press, NY; and Ngo (ed.) (1988) Non-isotopic Immunoassays Plenum Press, NY.

Immunoassays for measurement of these monocyte proteins can be performed by a variety of methods known to those skilled in the art. In brief, immunoassays to measure the protein can be competitive or noncompetitive binding assays. In competitive binding assays, the sample to be analyzed competes with a labeled analyte for specific binding sites on a capture agent bound to a solid surface. Preferably the capture agent is an antibody specifically reactive with the monocyte

protein produced as described above. The concentration of labeled analyte bound to the capture agent is inversely proportional to the amount of free analyte present in the sample.

5 In a competitive binding immunoassay, the monocyte protein present in the sample competes with labeled protein for binding to a specific binding agent, for example, an antibody specifically reactive with the monocyte protein. The binding agent may be bound to a solid surface to effect separation of bound labeled protein from the unbound labeled protein. Alternately, the competitive binding assay may be
10 conducted in liquid phase and any of a variety of techniques known in the art may be used to separate the bound labeled protein from the unbound labeled protein. Following separation, the amount of bound labeled protein is determined. The amount of protein present in the sample is inversely proportional to the amount of labeled protein
15 binding.

Alternatively, a homogeneous immunoassay may be performed in which a separation step is not needed. In these immunoassays, the label on the protein is altered by the binding of the protein to its specific binding agent. This alteration in the labeled protein results in a decrease
20 or increase in the signal emitted by label, so that measurement of the label at the end of the immunoassay allows for detection or quantitation of the protein.

These monocyte proteins may also be quantitatively determined by a variety of noncompetitive immunoassay methods. For example, a
25 two-site, solid phase sandwich immunoassay may be used. In this type of assay, a binding agent for the protein, for example an antibody, is attached to a solid support. A second protein binding agent, which may also be an antibody, and which binds the protein at a different site, is labeled. After binding at both sites on the protein has occurred, the
30 unbound labeled binding agent is removed and the amount of labeled binding agent bound to the solid phase is measured. The amount of labeled binding agent bound is directly proportional to the amount of protein in the sample.

Western blot analysis can be used to determine the presence of
35 monocyte proteins in a sample. Electrophoresis is carried out, e.g., on a tissue sample suspected of containing the protein. Following electrophoresis to separate the proteins, and transfer of the proteins to a suitable solid support such as a nitrocellulose filter, the solid support is incubated with an antibody reactive with the denatured protein. This

antibody may be labeled, or alternatively may be it may be detected by subsequent incubation with a second labeled antibody that binds the primary antibody.

5 The immunoassay formats described above employ labeled assay components. The label can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labeled by any one of several methods. Traditionally a radioactive label incorporating ^3H , ^{125}I , ^{35}S ,
10 ^{14}C , or ^{32}P is used. Non-radioactive labels include ligands which bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labeled protein. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available
15 instrumentation. For a review of various labeling or signal producing systems which may be used, see U.S. Patent No. 4,391,904, which is incorporated herein by reference.

20 Antibodies reactive with a particular protein can also be measured by a variety of immunoassay methods. For reviews of immunological and immunoassay procedures applicable to the measurement of antibodies by immunoassay techniques, see, e.g., Stites and Terr (eds.) Basic and Clinical Immunology (7th ed.) supra; Maggio (ed.) Enzyme Immunoassay, supra; and Harlow and Lane Antibodies, A Laboratory Manual, supra.

25 A variety of different immunoassay formats, separation techniques, and labels can be also be used similar to those described above for the measurement of specific proteins. Moreover, many methods are known for evaluating selectivity of binding for specific protein or closely related proteins.

30 VI. Purified monocyte proteins

The human monocyte FDF03 protein amino acid sequence is provided in SEQ ID NO: 2. Partial mouse sequence is provided in SEQ ID NO: 4. Human YE01 amino acid and nucleotide sequences for the Ig-
35 family member are provided in SEQ ID NO: 5-10. The receptor family members, designated KTE03, are described in SEQ ID NO: 11-22.

The peptide sequences allow preparation of peptides to generate antibodies to recognize such segments, and allow preparation of oligonucleotides which encode such sequences. Moreover, affinity

reagents allow detection and purification of more protein, including full length or recombinant forms. And oligonucleotide sequences allow detection of cDNAs encoding, or closely related to, these.

VII. Physical Variants

This invention also encompasses proteins or peptides having substantial amino acid sequence similarity with an amino acid sequence of a SEQ ID NO: 2 or 4; 6, 8, or 10; or 12, 14, 16, 18, 20 or 22, especially splice variants. Variants exhibiting substitutions, e.g., 20 or fewer, preferably 10 or fewer, and more preferably 5 or fewer substitutions, are also enabled. Where the substitutions are conservative substitutions, the variants will share immunogenic or antigenic similarity or cross-reactivity with a corresponding natural sequence protein. Natural variants include individual, allelic, polymorphic, strain, or species variants.

Amino acid sequence similarity, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences include natural allelic and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 50-100% similarity (if gaps can be introduced), to 75-100% similarity (if conservative substitutions are included) with the amino acid sequence of the relevant monocyte protein. Identity measures will be at least about 50%, generally at least 60%, more generally at least 65%, usually at least 70%, more usually at least 75%, preferably at least 80%, and more preferably at least 80%, and in particularly preferred embodiments, at least 85% or more. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison Chapter One, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI.

Nucleic acids encoding the corresponding mammalian monocyte proteins will typically hybridize, e.g., to SEQ ID NO 1 and/or 3; 5, 7,

and/or 9; or 11, 13, 15, 17, 19 and/or 21 under stringent conditions. For example, nucleic acids encoding the respective monocyte proteins will typically hybridize to the appropriate nucleic acid under stringent hybridization conditions, while providing few false positive
5 hybridization signals. Generally, stringent conditions are selected to be about 10° C lower than the thermal melting point (T_m) for the sequence being hybridized to at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Typically,
10 stringent conditions will be those in which the salt concentration in wash is about 0.02 molar at pH 7 and the temperature is at least about 50° C. Other factors may significantly affect the stringency of hybridization, including, among others, base composition and size of the complementary strands, the presence of organic solvents such as
15 formamide, and the extent of base mismatching. A preferred embodiment will include nucleic acids which will bind to disclosed sequences in 50% formamide and 20-50 mM NaCl at 42° C. In certain cases, the stringency may be relaxed to detect other nucleic acids exhibiting less than complete sequence identity.

20 An isolated monocyte gene DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode these monocyte antigens, their derivatives, or proteins having highly similar physiological,
25 immunogenic, or antigenic activity.

Modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant monocyte protein derivatives include
30 predetermined or site-specific mutations of the respective protein or its fragments. "Mutant monocyte protein" encompasses a polypeptide otherwise falling within the homology definition of the monocyte protein as set forth above, but having an amino acid sequence which differs from that of the monocyte protein as found in nature, whether by
35 way of deletion, substitution, or insertion. In particular, "site specific mutant monocyte protein" generally includes proteins having significant similarity with a protein having a sequence of SEQ ID NO: 2 or 4; 6, 8, or 10; or 12, 14, 16, 18, 20 or 22. Generally, the variant will share many physiochemical and biological activities, e.g., antigenic or

immunogenic, with those sequences, and in preferred embodiments contain most or all of the disclosed sequence. Similar concepts apply to these various monocyte proteins, particularly those found in various warm blooded animals, e.g., primates and mammals.

5 Although site specific mutation sites are predetermined, mutants need not be site specific. Monocyte protein mutagenesis can be conducted by making amino acid insertions or deletions. Substitutions, deletions, insertions, or any combinations may be generated to arrive at a final construct. Insertions include amino- or carboxyl- terminal
10 fusions. Random mutagenesis can be conducted at a target codon and the expressed mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis or polymerase chain reaction (PCR) techniques. See
15 also, Sambrook, et al. (1989) and Ausubel, et al. (1987 and Supplements). The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

20 The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of an immunoglobulin with a respective monocyte polypeptide
25 is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

30 In addition, new constructs may be made from combining similar functional domains from other proteins. For example, domains or other segments may be "swapped" between different new fusion polypeptides or fragments, typically with related proteins, e.g., within the Ig family or the Fc receptor family. Preferably, intact structural domains will be used, e.g., intact Ig portions. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem.
35 263:15985-15992. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of protein-binding specificities and other functional domains. Also, alanine scanning mutagenesis may be applied, preferably to residues

which structurally are exterior to the secondary structure, which will avoid most of the critical residues which generally disrupt tertiary structure.

5 "Derivatives" of these monocyte antigens include amino acid sequence mutants, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in these monocyte protein amino acid side chains or at the N- or C-termini, by means which are well known in the art. These derivatives
10 can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected
15 from the group of alkyl-moieties including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species. Covalent attachment to carrier proteins may be important when immunogenic moieties are haptens.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its
20 synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are
25 versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine, or other moieties, including ribosyl groups or cross-linking reagents. Also, proteins comprising substitutions are encompassed, which should
30 retain substantial immunogenicity, to produce antibodies which recognize a protein of SEQ ID NO: 2 or 4; 6, 8, or 10; or 12, 14, 16, 18, 20 or 22. Alternatively, it may be desired to produce antibodies which recognize both SEQ ID NO: 2 and 4; 6, 8, and 10; or 12, 14, 16, 18, 20 or 22. Typically, these proteins will contain less than 20 residue substitutions
35 from the disclosed sequence, more typically less than 10 substitutions, preferably less than 5, and more preferably less than 3. Alternatively, proteins which begin and end at structural domains will usually retain antigenicity and cross immunogenicity.

A major group of derivatives are covalent conjugates of the monocyte proteins or fragments thereof with other proteins or polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred protein derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between these monocyte proteins and other homologous or heterologous proteins are also provided. Heterologous polypeptides may be fusions between different surface markers, resulting in, e.g., a hybrid protein. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a receptor-binding segment, so that the presence or location of the fused protein may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609. Other gene fusion partners include bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) *Science* 241:812-816.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

This invention also contemplates the use of derivatives of these monocyte proteins other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into the three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of ligands or other binding ligands. For example, a monocyte protein antigen can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed

onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of anti-monocyte protein antibodies. The monocyte proteins can also be labeled with a detectable group, e.g., radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays. Purification of these monocyte proteins may be effected by immobilized antibodies.

Isolated monocyte protein genes will allow transformation of cells lacking expression of a corresponding monocyte protein, e.g., either species types or cells which lack corresponding proteins and exhibit negative background activity. Expression of transformed genes will allow isolation of antigenically pure cell lines, with defined or single specie variants. This approach will allow for more sensitive detection and discrimination of the physiological effects of these monocyte proteins. Subcellular fragments, e.g., cytoplasts or membrane fragments, can be isolated and used.

VIII. Binding Agent: Monocyte Protein Complexes

A monocyte protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 2 and/or 4; 6, 8, and/or 10; or 12, 14, 16, 18, 20 and/or 22 is determined in an immunoassay. The immunoassay uses a polyclonal antiserum which was raised to the protein of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22 or appropriate combination. This antiserum is selected to have low crossreactivity against other members of the related families, and any such crossreactivity is, or may be, removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22 is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An inbred strain of mice such as Balb/c is immunized with the appropriate protein using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid

support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other related proteins, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. See also Hertenzenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols 1-4, Blackwell Science; and Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY. Preferably two different related proteins are used in this determination in conjunction with a given monocyte protein. For example, with the Ig family protein, at least two other family members are used to absorb out shared epitopes. In conjunction with the Fc family member, two other members of the family are used. These other family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO 2 and/or 4; 6, 8, and/or 10; or 12, 14, 16, 18, 20 or 22. The percent crossreactivity for the above proteins is calculated using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the monocyte protein of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein, e.g., of SEQ ID NO: 2, that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that monocyte proteins are each a family of homologous proteins that comprise two or more genes. For a particular

gene product, such as the human Ig family member protein, the invention encompasses not only the amino acid sequences disclosed herein, but also to other proteins that are allelic, polymorphic, non-allelic, or species variants. It also understood that the term "human monocyte protein" includes nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding these proteins or splice variants from the gene, or by substituting or adding small numbers of new amino acids. Such minor alterations must substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring respective monocyte protein, for example, the human monocyte protein exhibiting SEQ ID NO: 4. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for each protein family as a whole. By aligning a protein optimally with the protein of SEQ ID NO 2 and 4; 6, 8, and 10; or 12, 14, 16, 18, 20 and 22 and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

IX. Uses

The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for developmental abnormalities, or below in the description of kits for diagnosis.

Monocyte genes, e.g., DNA or RNA may be used as a component in a forensic assay. For instance, the nucleotide sequences provided may be labeled using, e.g., ^{32}P or biotin and used to probe standard restriction fragment polymorphism blots, providing a measurable character to aid in distinguishing between individuals. Such probes may be used in well-known forensic techniques such as genetic fingerprinting. In addition, nucleotide probes made from monocyte sequences may be used in in situ assays to detect chromosomal abnormalities.

Antibodies and other binding agents directed towards monocyte proteins or nucleic acids may be used to purify the corresponding monocyte protein molecule. As described in the Examples below, antibody purification of monocyte proteins is both possible and

practicable. Antibodies and other binding agents may also be used in a diagnostic fashion to determine whether monocyte components are present in a tissue sample or cell population using well-known techniques described herein. The ability to attach a binding agent to a monocyte protein provides a means to diagnose disorders associated with expression misregulation. Antibodies and other monocyte protein binding agents may also be useful as histological markers. As described in the examples below, the expression of each of these proteins is limited to specific tissue types. By directing a probe, such as an antibody or nucleic acid to the respective monocyte protein, it is possible to use the probe to distinguish tissue and cell types in situ or in vitro.

This invention also provides reagents which may exhibit significant therapeutic value. The monocyte proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to the monocyte protein, may be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a monocyte, e.g., as an antigen presenting cell, is a target for an agonist or antagonist of the protein. The proteins likely play a role in regulation or development of hematopoietic cells, e.g., lymphoid cells, which affect immunological responses, e.g., antigen presentation and the resulting effector functions.

For example, the DX26 antibody shows that inhibitory antibodies will be useful in modulating NK or T cell functions, e.g., killing. Such modulation will typically be a 20% effect, either increasing or decreasing, e.g., the killing effect, but in preferred embodiments will have a 30%, 40%, 50%, or more. Because the distribution is also in monocytes, the molecule will probably also affect the regulation of monocyte mediated or initiated effector functions of the immune system, e.g., autoimmune responses, transplantation rejection, graft vs. host disease, inflammatory conditions, etc. These molecules may also affect elimination of neoplastic conditions, e.g., tumor rejection.

Other abnormal developmental conditions are known in cell types shown to possess monocyte protein mRNA by northern blot

analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, NJ; and Thorn, et al. Harrison's Principles of Internal Medicine, McGraw-Hill, NY. Developmental or functional abnormalities, e.g., of the immune system, cause significant medical abnormalities and conditions which may be susceptible to prevention or treatment using compositions provided herein.

Recombinant monocyte proteins or antibodies might be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers and excipients. In particular, these may be useful in a vaccine context, where the antigen is combined with one of these therapeutic versions of agonists or antagonists. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

Drug screening using antibodies or receptor or fragments thereof can identify compounds having binding affinity to these monocyte proteins, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the protein. Likewise, a compound having intrinsic stimulating activity might activate the cell through the protein and is thus an agonist in that it simulates the cell. This invention further contemplates the therapeutic use of antibodies to the proteins as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicaments administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and

(1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, NJ. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous administration.

The monocyte proteins, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, could be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention

may be combined with or used in association with other chemotherapeutic or chemopreventive agents.

Both the naturally occurring and the recombinant form of the monocyte proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period. See, e.g., Fodor, et al. (1991) Science 251:767-773, and other descriptions of chemical diversity libraries, which describe means for testing of binding affinity by a plurality of compounds. The development of suitable assays can be greatly facilitated by the availability of large amounts of purified, e.g., soluble versions of, monocyte protein as provided by this invention.

For example, antagonists can often be found once the protein has been structurally defined. Testing of potential protein analogs is now possible upon the development of highly automated assay methods using a purified surface protein. In particular, new agonists and antagonists will be discovered by using screening techniques described herein. Of particular importance are compounds found to have a combined binding affinity for multiple related cell surface antigens, e.g., compounds which can serve as antagonists for species variants of a monocyte protein.

This invention is particularly useful for screening compounds by using recombinant monocyte protein in a variety of drug screening techniques. The advantages of using a recombinant protein in screening for specific ligands include: (a) improved renewable source of the protein from a specific source; (b) potentially greater number of antigens per cell giving better signal to noise ratio in assays; and (c) species variant specificity (theoretically giving greater biological and disease specificity).

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing a monocyte protein. Cells may be isolated which express that protein in isolation from any others. Such cells, either in viable or fixed form, can be used for standard surface protein binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of monocyte protein) are contacted and

incubated with an antibody having known binding affinity to the antigen, such as ^{125}I -antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of protein binding. The amount of test compound bound is inversely proportional to the amount of labeled antibody binding to the known source. Many techniques can be used to separate bound from free reagent to assess the degree of binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on these monocyte protein mediated functions, e.g., antigen presentation or helper function.

Another method utilizes membranes from transformed eukaryotic or prokaryotic host cells as the source of a monocyte protein. These cells are stably transformed with DNA vectors directing the expression of the appropriate protein, e.g., an engineered membrane bound form. Essentially, the membranes would be prepared from the cells and used in binding assays such as the competitive assay set forth above.

Still another approach is to use solubilized, unpurified or solubilized, purified monocyte protein from transformed eukaryotic or prokaryotic host cells. This allows for a "molecular" binding assay with the advantages of increased specificity, the ability to automate, and high drug test throughput.

Another technique for drug screening involves an approach which provides high throughput screening for compounds having suitable binding affinity to the respective monocyte protein and is described in detail in Geysen, European Patent Application 84/03564, published on September 13, 1984. First, large numbers of different small peptide test compounds are synthesized on a solid substrate, e.g., plastic pins or some other appropriate surface, see Fodor, et al., supra. Then all the pins are reacted with solubilized, unpurified or solubilized, purified monocyte protein, and washed. The next step involves detecting bound reagent, e.g., antibody.

One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact

regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography Academic Press, NY.

5 X. Kits

This invention also contemplates use of these monocyte proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of a monocyte protein or message. Typically the kit will have a compartment
10 containing either a defined monocyte peptide or gene segment or a reagent which recognizes one or the other, e.g., antibodies.

A kit for determining the binding affinity of a test compound to the respective monocyte protein would typically comprise a test compound; a labeled compound, for example an antibody having
15 known binding affinity for the protein; a source of the monocyte protein (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as a solid phase for immobilizing the monocyte protein. Once compounds are screened, those having suitable binding affinity to the protein can be evaluated in suitable biological
20 assays, as are well known in the art, to determine whether they act as agonists or antagonists to regulate monocyte function. The availability of recombinant monocyte polypeptides also provide well defined standards for calibrating such assays.

A preferred kit for determining the concentration of, for example,
25 a monocyte protein in a sample would typically comprise a labeled compound, e.g., antibody, having known binding affinity for the monocyte protein, a source of monocyte protein (naturally occurring or recombinant) and a means for separating the bound from free labeled compound, for example, a solid phase for immobilizing the monocyte
30 protein. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, specific for the respective monocyte or its fragments are useful in diagnostic applications to detect the presence of elevated levels of the protein
35 and/or its fragments. Such diagnostic assays can employ lysates, live cells, fixed cells, immunofluorescence, cell cultures, body fluids, and further can involve the detection of antigens in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and antigen-monocyte protein complex) or

heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA), and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to the monocyte protein or to a particular fragment thereof. Similar assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press, NY; Chan (ed.) (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassay Stockton Press, NY; and Ngo (ed.) (1988) Nonisotopic Immunoassay Plenum Press, NY. In particular, the reagents may be useful for diagnosing monocyte populations in biological samples, either to detect an excess or deficiency of monocyte in a sample. The assay may be directed to histological analysis of a biopsy, or evaluation of monocyte numbers in a blood or tissue sample.

Anti-idiotypic antibodies may have similar use to diagnose presence of antibodies against a monocyte protein, as such may be diagnostic of various abnormal states. For example, overproduction of the monocyte protein may result in various immunological reactions which may be diagnostic of abnormal physiological states, particularly in proliferative cell conditions such as cancer or abnormal differentiation.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody or receptor, or labeled monocyte protein is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium providing appropriate concentrations of reagents for performing the assay.

Many of the aforementioned constituents of the drug screening and the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by

covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, the protein, test compound, monocyte protein, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free protein, or alternatively the bound from the free test compound. The monocyte protein can be immobilized on various matrices followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the monocyte protein to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of protein/antibody complex by one of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678.

Methods for linking proteins or their fragments to the various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of a respective monocyte protein. These sequences can be used as probes for detecting levels of the message in samples from patients suspected of having an abnormal condition, e.g., cancer or immune problem. The preparation of both RNA and DNA nucleotide sequences, the labeling of

the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorophores, enzymes, or the like.

Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in any conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

XI. Binding Partner Isolation

Having isolated one member of a binding partner of a specific interaction, methods exist for isolating the counter-partner. See, Gearing, et al. (1989) EMBO J. 8:3667-3676. For example, means to label a monocyte surface protein without interfering with the binding to its receptor can be determined. For example, an affinity label can be fused to either the amino- or carboxyl-terminus of the ligand. An expression library can be screened for specific binding to the monocyte protein, e.g., by cell sorting, or other screening to detect subpopulations which express such a binding component. See, e.g., Ho, et al. (1993) Proc. Nat'l Acad. Sci. USA 90:11267-11271. Alternatively, a panning method may be used. See, e.g., Seed and Aruffo (1987) Proc. Nat'l Acad. Sci. USA 84:3365-3369.

A two-hybrid selection system may also be applied making appropriate constructs with the available monocyte protein sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Protein cross-linking techniques with label can be applied to isolate binding partners of a monocyte protein. This would allow identification of proteins which specifically interact with the appropriate monocyte protein.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLES

I. General Methods

Many of the standard methods below are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.) Vols. 1-3, CSH Press, NY; Ausubel, et al., Biology Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology Wiley/Greene, NY; Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications Academic Press, NY.

Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification," Methods in Enzymology vol. 182, and other volumes in this series; Coligan, et al. (1996 and periodic Supplements) Current Protocols in Protein Science Wiley/Greene, NY; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, NJ, or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, NY; and Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Standard immunological techniques are described, e.g., in Hertenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163. See also, e.g., Paul (ed.) (1993) Fundamental Immunology (3d ed.) Raven Press, N.Y.

FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY.

II. Isolation of human monocytes

Healthy donors were subjected to a leukapheresis. Percoll gradients were used to isolate mononuclear cells which were then subject to centrifugal elutriation. See, Figdor, et al. (1982) Blood 60:46-53; and Plas, et al. (1988) Expt'l. Hematol. 16:355-359. This highly enriched monocyte fraction was cultured for 5-7 days in the presence of GM-CSF (800 U/ml) and IL-4 (500 U/ml), as described in Romani, et al (1994) J. Exp. Med. 180:83-93; and Sallusto, et al (1994) J. Exp. Med. 179:1109-1118.

For making dendritic cells, human CD34+ cells were obtained as follows. See, e.g., Caux, et al. (1995) pages 1-5 in Banchereau and Schmitt Dendritic Cells in Fundamental and Clinical Immunology Plenum Press, NY. Peripheral or cord blood cells, sometimes CD34+ selected, were cultured in the presence of Stem Cell Factor (SCF), GM-CSF, and TNF- α in endotoxin free RPMI 1640 medium (GIBCO, Grand Island, NY) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS; Flow Laboratories, Irvine, CA), 10 mM HEPES, 2 mM L-glutamine, 5×10^{-5} M 2-mercaptoethanol, penicillin (100 mg/ml). This is referred to as complete medium.

CD34+ cells were seeded for expansion in 25 to 75 cm² flasks (Corning, NY) at 2×10^4 cells/ml. Optimal conditions were maintained by splitting these cultures at day 5 and 10 with medium containing fresh GM-CSF and TNF- α (cell concentration: $1-3 \times 10^5$ cells/ml). In certain cases, cells were FACS sorted for CD1a expression at about day 6.

In certain situations, cells were routinely collected after 12 days of culture, eventually adherent cells were recovered using a 5 mM EDTA solution. In other situations, the CD1a+ cells were activated by resuspension in complete medium at 5×10^6 cells/ml and activated for

the appropriate time (e.g., 1 or 6 h) with 1 mg/ml phorbol 12-myristate 13-acetate (PMA, Sigma) and 100 ng/ml ionomycin (Calbiochem, La Jolla, CA). These cells were expanded for another 6 days, and RNA isolated for cDNA library preparation.

III. RNA isolation and library construction

Total RNA is isolated using, e.g., the guanidine thiocyanate/CsCl gradient procedure as described by Chirgwin, et al. (1978) Biochem. 18:5294-5299.

Alternatively, poly(A)+ RNA is isolated using the OLIGOTEX mRNA isolation kit (QIAGEN). Double stranded cDNA are generated using, e.g., the SUPERScript plasmid system (Gibco BRL, Gaithersburg, MD) for cDNA synthesis and plasmid cloning. The resulting double stranded cDNA is unidirectionally cloned, e.g., into pSport1 and transfected by electroporation into ELECTROMAX DH10BTM Cells (Gibco BRL, Gaithersburg, MD).

IV. Sequencing

DNA isolated from randomly picked clones, or after subtractive hybridization using unactivated cells, were subjected to nucleotide sequence analysis using standard techniques. A Taq DiDeoxy Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA) can be used. The labeled DNA fragments are separated using a DNA sequencing gel of an appropriate automated sequencer. Alternatively, the isolated clone is sequenced as described, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Chemical sequencing methods are also available, e.g., using Maxam and Gilbert sequencing techniques.

V. Isolation of human monocyte protein genes

The FDF03, the YE01, and KTE03 (YYB01 and YYB04) clones were sequenced, and analyzed for open reading frames. The clones were further analyzed to extend the nucleic acid sequence to a full, or nearly full, open reading frame.

mRNA is prepared from appropriate cell populations by the FastTrack kit (Invitrogen) from which cDNA is generated using, e.g., SuperScript Plasmid System for cDNA synthesis from GIBCO-BRL (Gaithersburg, MD) essentially as described by the manufacturer.

5 Modification to the procedure may include the substitution of other cloning adapters for the SalI adapters provided with the kit. The resultant cDNA from these cells is used to generate libraries, e.g., in the plasmid PCDNA II (Invitrogen). The cDNA is cloned into the polylinker and is used to transform an appropriate strain, e.g., DH10B, of

10 E. coli. Plasmid is isolated and purified, e.g., with the Qiagen system (Chatsworth, CA) which is used to generate RNA probes from, e.g., the SP6 promoter.

RNA probes are labeled, e.g., using the Genius System (Boehringer-Mannheim) as described by the manufacturer. Filter lifts of

15 the cDNA library can be pre-hybridized, e.g., at 42° C for 3-6 hours in Church's buffer (50% formamide, 6X SSPE, 50 mM NaHPO₄ pH 7.2, 7% SDS, 0.1% N-Lauryl sarcosine, 2% Boehringer-Mannheim blocking reagent). Filters are probed, e.g., overnight in the same buffer containing the appropriate probes. The filters are washed, e.g., as

20 described by the Genius System. The colonies that hybridize are selected.

The entire cDNA of human monocyte proteins are sequenced, e.g., by the dideoxynucleotide chain termination method with T7 polymerase (U.S. Biochemicals, Cleveland, OH) using double-stranded DNA as template. Data base searching and sequence analysis are

25 performed using IntelliGenetics programs (Mountain View, CA) to determine if homology exists between previously reported clones.

SEQ ID NOs: 1-4 disclose sequences relating to a human FDF03 gene and mouse counterpart sequences. Likewise, SEQ ID NOs: 5-10 set forth sequences relating to human YE01 gene products, including a

30 splice variant and a transcript which encodes a soluble product. SEQ ID NOs 11-22 provide sequences of embodiments of the KTE03 gene products, and shows evidence of splice variants.

VI. Recombinant monocyte gene constructs

35 Poly(A)⁺ RNA is isolated from appropriate cell populations, e.g., using the FastTrack mRNA kit (Invitrogen, San Diego, CA). Samples are electrophoresed, e.g., in a 1% agarose gel containing formaldehyde and transferred to a GeneScreen membrane (NEN Research Products, Boston, MA). Hybridization is performed, e.g., at 65° C in 0.5 M

NaHPO₄ pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V) with ³²P-dCTP labeled monocyte gene cDNA at 10⁷ cpm/ml. After hybridization filters are washed three times at 50° C in 0.2X SSC, 0.1% SDS, and exposed to film for 24 h.

5 The recombinant gene construct may be used to generate probe for detecting the message. The insert may be excised and used in the detection methods described above.

VII. Expression of monocyte gene protein in E. coli.

10 PCR is used to make a construct comprising the open reading frame, preferably in operable association with proper promoter, selection, and regulatory sequences. The resulting expression plasmid is transformed into an appropriate, e.g., the Topp5, E. coli strain (Stratagene, La Jolla, CA). Ampicillin resistant (50 µg/ml) transformants
15 are grown in Luria Broth (Gibco) at 37° C until the optical density at 550 nm is 0.7. Recombinant protein is induced with 0.4 mM isopropyl-bD-thiogalacto-pyranoside (Sigma, St. Louis, MO) and incubation of the cells continued at 20° C for a further 18 hours. Cells from a 1 liter culture are harvested by centrifugation and resuspended, e.g., in 200 ml of ice cold
20 30% sucrose, 50 mM Tris HCl pH 8.0, 1 mM ethylenediamine-tetraacetic acid. After 10 min on ice, ice cold water is added to a total volume of 2 liters. After 20 min on ice, cells are removed by centrifugation and the supernatant is clarified by filtration via a 5 µM Millipak 60 (Millipore Corp., Bedford, MA).

25 The recombinant protein is purified via standard purification methods, e.g., various ion exchange chromatography methods. Immunoaffinity methods using antibodies described below can also be used. Affinity methods may be used where an epitope tag is engineered into an expression construct.

VIII. Mapping of human monocyte genes

30 DNA isolation, restriction enzyme digestion, agarose gel electrophoresis, Southern blot transfer and hybridization are performed according to standard techniques. See Jenkins, et al. (1982) J. Virol.
35 43:26-36. Blots may be prepared with Hybond-N nylon membrane (Amersham). The probe is labeled with ³²P-dCTP; washing is done to a final stringency, e.g., of 0.1X SSC, 0.1% SDS, 65° C.

 Alternatively, a BIOS Laboratories (New Haven, CT) mouse somatic cell hybrid panel may be combined with PCR methods.

IX. Analysis of individual variation

From the distribution data, an abundant easily accessible cell type is selected for sampling from individuals. Using PCR techniques, a large population of individuals are analyzed for this gene. cDNA or other PCR methods are used to sequence the corresponding gene in the different individuals, and their sequences are compared. This indicates both the extent of divergence among racial or other populations, as well as determining which residues are likely to be modifiable without dramatic effects on function.

X. Preparation of Antibodies

Recombinant monocyte proteins are generated by expression in *E. coli* as shown above, and tested for biological activity. Active or denatured proteins may be used for immunization of appropriate mammals for either polyclonal serum production, or for monoclonal antibody production. Antibodies are selected for use in Western blots, against native or denatured antigen, and for those which modulate a biological activity.

XI. Isolation of counterpart primate monocyte genes

Human cDNA clones encoding these genes are used as probes, or to design PCR primers to find counterparts in various primate species, e.g., chimpanzees.

XII. Use of reagents to analyze cell populations

Detection of the level of monocyte cells present in a sample is important for diagnosis of certain aberrant disease conditions. For example, an increase in the number of monocytes in a tissue or the lymph system can be indicative of the presence of a monocyte hyperplasia, tissue or graft rejection, or inflammation. A low monocyte population can indicate an abnormal reaction to, e.g., a bacterial or viral infection, which may require the appropriate treat to normalize the monocyte response.

FACS analysis using a labeled binding agent specific for a cell surface monocyte protein, see, e.g., Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY, is

used in determining the number of monocytes present in a cell mixture, e.g., PBMCs, adherent cells, etc. The binding agent is also used for histological analysis of tissue samples, either fresh or fixed, to analyze infiltration of monocyte. Diverse cell populations may also be evaluated, either in a cell destructive assay, or in certain assays where cells retain viability.

Analysis of the presence of soluble intracellular molecules is performed, e.g., with a fluorescent binding agent specific for a monocyte as described in Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367.

alternatively, tissue or cell fixation methods may be used.

Levels of monocyte transcripts are quantitated, e.g., using semiquantitative PCR as described in Murphy, et al. (1993) J. Immunol. Methods 162:211-223. Primers are designed such that genomic DNA is not detected.

Distribution of the FDF03 embodiment has been studied using hybridization and PCR analysis. Northern blot analysis located transcripts in dendritic cells and the JY cell line. There appear to be two transcripts of about 700 bp and 1300 bp, which may be differentially regulated, and an estimated frequency of about 1 in 4000 in resting monocytes or LPS and IFNg activated monocytes. The shorter message does not appear to encode a soluble version of the protein, e.g., lacking the TM and intracellular segments. Southern blot analysis has detected transcripts in monocytes, dendritic cells, PBMC, B cells, and splenic B cells. The message appears to be down-regulated upon monocyte activation.

Distribution of the YE01 embodiment has also been evaluated. The message appears to be monocyte specific, and is a low abundance message. It is detectable in cDNA Southern blots in resting monocytes, and in activated monocytes. Its highest expression was found in 6 hour LPS stimulated monocytes. It is also detectable in anti-CD3 and PMA activated PBMC. It may be faintly detectable in dendritic cells, but this may be due to contamination of the dendritic cell population with residual monocytes. At that level of sensitivity, it is undetectable in NK cells, B or T cells, or any fetal cells examined. However, the YE01 gene product is specifically recognized by a monoclonal antibody DX26. This antibody, when crosslinked, can inhibit NK cell mediated killing of certain targets. The antibody recognizes protein expressed in T cells, B cells, NK cells, and monocytes. The gene encoding the antigen

recognized by DX26, which is apparently a polymorphic variant of the YE01 isolate, has been cloned and has essentially the sequence:

The KTE03 expression levels were also investigated. The message appeared to be up-regulated upon IL-10 exposure when the monocytes were activated by LPS and IFNg.

XIII. Isolation of a binding counterpart

A monocyte protein can be used as a specific binding reagent, by taking advantage of its specificity of binding, much like an antibody would be used. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The monocyte protein is used to screen for a cell line which exhibits binding. Standard staining techniques are used to detect or sort intracellular or surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at $2-3 \times 10^5$ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 mg/ml DEAE-dextran, 66 mM chloroquine, and 4 mg DNA in serum free DME. For each set, a positive control is prepared, e.g., of human receptor-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin(0.1%) with 32 ml/ml of 1M NaN₃ for 20 min. Cells are then washed with HBSS/saponin 1X. Add protein or protein/antibody complex to cells and incubate for 30 min. Wash cells

twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H₂O₂ per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Alternatively, other monocyte protein specific binding reagents are used to affinity purify or sort out cells expressing a receptor. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a monocyte protein fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of ligand expressing clones.

Phage expression libraries can be screened by monocyte protein. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

XIV. Isolation of a soluble YE01

An additional family member of the previously described YE01, also designated DNAX Leukocyte Associated Immunoglobulin-like Receptor (DLAIR; and now designated DLAIR-1) was cloned by screening a human T cell tumor line cDNA library (TcT). Bacterial colony lift membranes were hybridized with a DLAIR-1 probe comprising a BglII-SphI digestion fragment, spanning the Ig loop in the extracellular domain. Two positives were isolated and sequenced. Sequence analysis revealed that both clones contained identical open reading frames of 414 base pairs, encoding a 135 amino acid protein with a predicted 21 amino acid leader sequence and a predicted molecular weight of 14.7 kDa. This molecule, now referred to as DLAIR-2, contains

one Ig loop. The Ig loop has 84% homology with DLAIR-1, indicating that it belongs to the same family, but is encoded by a separate gene. DLAIR-2 lacks a transmembrane region which suggests that it is a secreted protein.

DLAIR-2, as a soluble molecule with similarity to DLAIR-1, may be used as an antagonist to this inhibitory receptor.

XV. Preparation of DX26 monoclonal antibody

Mice were immunized with a human NK cell clone and antibodies were screened for their capacity to inhibit NK cell-mediated lysis of FcR bearing targets. Alternatively, antibodies will be raised to purified protein.

XVI. Cross-linking DLAIR-1 with mAb inhibits NK cell-mediated killing

DX26 mAb did not inhibit NK clone killing of the HLA-negative EBV-transformed B cell line 721.221. However, when 721.221 was transfected with the human FcγR-II (CD32) and used as a target, NK cell-mediated cytotoxicity was inhibited by DX26 mAb. This indicates that signaling through the molecule recognized by DX26 mAb (designated DNAX Leukocyte Associated Immunoglobulin-like Receptor (DLAIR)), delivers a negative signal to NK cell clones that prevents their killing specific target cells. In agreement with this, NK cell-mediated cytotoxicity against Colo-205, PA-1, or FO-1, each an FcR-negative human cell line, was not inhibited by the addition of DX26 mAb. Moreover, lysis of P815 cells, an FcR-expressing mouse mastocytoma cell line, which is killed in vitro by human NK cell clones upon simultaneous cross linking of CD2, CD16, CD69, or DNAM-1 antigen, was also inhibited by DX26 mAb. These results lead to a conclusion that DLAIR delivers a strong inhibitory signal to NK cells, since the positive signal given by potent inducers of NK cell cytotoxicity was overruled by DX26 mAb.

XVII. DLAIR-1 is an inhibitory receptor on resting NK cells

NK cell clones consist of clonally derived populations of activated NK cells. These cells are potently inhibited by DLAIR signaling. We set out to study whether DLAIR is also functioning as an inhibitory receptor on NK cells that had not been previously activated. Resting NK cells, prepared from peripheral blood by negative depletion using magnetic beads, were able to lyse P815 target cells when simultaneously activated

through CD16. This NK cell mediated cytotoxicity was inhibited by the addition of DX26 mAb. Thus, DLAIR is functional as an inhibitory receptor on both activated and resting NK cells.

5 XVIII. DLAIR is a widely expressed antigen

Phenotypic analysis of human peripheral blood lymphocytes demonstrated that DLAIR is a widely distributed molecule. In healthy donor PBMC, CD3⁺CD4⁺ T cells (70-80%), CD3⁺CD8⁺ T cells (80-90%), CD3⁻CD56⁺ NK cells (95-100%), CD3⁻CD19⁺ B cells (80-90%), and CD3⁻CD14⁺ monocytes (99-100%) all expressed the DLAIR molecule. Human fetal thymocytes, both the immature CD4⁺CD8⁺ cells and mature CD4⁺CD8⁻ or CD4⁻CD8⁺ single positive cells also expressed DLAIR. Peripheral blood granulocytes, platelets and erythrocytes did not express DLAIR.

15 Human NK cell clones and T cell clones all expressed DLAIR, with the exception of the long-term cultured NK clones NKL and NK92 (see Table 2). EBV-transformed B cell lines, the B cell tumor Daudi, and the NK tumor cell line YT and several non-hematopoietic cell lines did not express DLAIR, whereas human T cell lines did show DLAIR
20 expression.

Table 2: Expression of DLAIR on human tumor cell lines¹

cell line	type	control IgG1 (mean fluorescence intensity)	DX26 mAb
HUT78	T cell tumor	<5	25.8
Peer	T cell tumor	<5	29.1
Molt4	T cell tumor	<5	30.7
CEM	T cell tumor	<5	92.7
Jurkat	T cell tumor	<5	47.1
HL60	promyeloid tumor	<5	46.9
U937	myeloid tumor	<5	49.5
721.221	EBV- B cell	<5	<5
JY	EBV- B cell	<5	<5
Daudi	B ⁻ cell tumor	<5	<5
YT	NK cell tumor	<5	<5
NKL	NK cell clone	<5	<5
NK92	NK cell clone	<5	<5
Colo205	colon carcinoma	<5	<5
293T	embryonic kidney	<5	<5

PA-1	teratocarcinoma	<5	<5
FO-1	melanoma	<5	<5

¹cells were stained with control IgG1 or DX26 mAb and PE-conjugated goat-anti-mouse-IgG as a second step. Cells were analyzed on a FACScan.

5 XIX. Expression cloning of the DX26 antigen

The DX26 antibody was used to expression clone the antigen the antibody recognizes. The expression cloning was performed using standard methods. See, e.g., Sambrook, et al. or Coligan, et al.

10 DX26 antigen is expression cloned, e.g., from a polyclonal human activated NK cell cDNA library in the pJFE14 expression vector. COS7 cells are transfected with the library and antigen positive cells were selected using phycoerythrin labeled anti-DX26 mAb. The cDNA sequence was determined and found to match much of the YE01 sequence. The DX26 antibody specifically binds to the product of the
15 YE01 gene product.

In another method, oligonucleotides are used to screen a library. In combination with polymerase chain reaction (PCR) techniques, synthetic oligonucleotides in appropriate orientations are used as primers to select correct clones from a library.

20 Moreover, the YE01 gene product is specifically recognized by a monoclonal antibody DX26. This antibody, when crosslinked, can inhibit NK cell mediated killing of certain targets. The antibody recognizes protein expressed in T cells, B cells, NK cells, and monocytes. The gene encoding the antigen recognized by DX26, which is apparently
25 a polymorphic variant of the YE01 isolate, has been cloned and has essentially the sequence (see SEQ ID NO: 7). This isolate has a different 3' untranslated sequence from the original YE01 transcript, apparently due to use of an alternative polyadenylation site. A soluble form of DLAIR has also been detected (see SEQ ID NO: 9).

30 Distribution analysis of the DX26 isolate has determined, Northern blot analysis, the distribution as follows. Probing of mRNA of human NK cell clones with DLAIR cDNA, PBMC, the human T cell line Jurkat, and the human myeloid cell line Jurkat results in two bands of approximately 1800 bp and 3000-4000 bp. This indicates that besides the
35 cloned cDNA, another transcript with sequence similarity to DLAIR exists in these cell lines. Whether this contains the same open reading frame is at present unknown, but will be determined upon cloning and
56

sequence analysis of that transcript. The EBV-transformed human B cell line JY did not show transcripts that probed with DLAIR cDNA.

XX. DLAIR-1 Binds SHP-1 and SHP-2

5 The existence of two consensus sequences for ITIMs within the cytoplasmic domain of DLAIR-1, suggested that the generation of an inhibitory signal in NK cells was manifested by the recruitment of SHP-1 and/or SHP-2. To determine if DLAIR-1 was capable of binding protein tyrosine phosphatases, a NK cell clone was stimulated with pervanadate (an inhibitor of protein tyrosine phosphatases that induces
10 tyrosine phosphorylation (O'Shea, et al. (1992) Proc. Natl. Acad. Sci. USA 89:10306-10310), lysed, and immunoprecipitated with DX26 MAb. Immunoprecipitates were then analyzed by Western blot using antibodies specific for SHP-1 and SHP-2. Both SHP-1 and SHP-2 associated with tyrosine phosphorylated DLAIR-1. These results suggest
15 that recruitment of SHP-1 and SHP-2 may be involved in mediating the negative signal transduced via engagement of the DLAIR-1 molecule.

20 All references cited herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

25 Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

SEQUENCE SUBMISSION

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Schering Corp.
(B) STREET: 2000 Galloping Hill Road
(C) CITY: Kenilworth
(D) STATE: New Jersey
(E) COUNTRY: USA
(F) ZIP: 07033

(ii) TITLE OF INVENTION: Isolated Mammalian Monocyte Cell Genes;
Related Reagents

(iii) NUMBER OF SEQUENCES: 22

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
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(v) CURRENT APPLICATION DATA:

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(vi) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 08/762,187
(B) FILING DATE: 09-DEC-1996

(vi) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 60/033,181
(B) FILING DATE: 16-DEC-1996

(vi) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 60/041,279
(B) FILING DATE: 21-MAR-1997

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1249 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 154..1062

(ix) FEATURE:

(A) NAME/KEY: mat_peptide

(B) LOCATION: 211..1062

5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:	
	GT TTG GGG GAA GG CTCTCTGGC CCCCACAGCC CTCTTCGGAG CCTGAGCCCG GCTCTCCTCA	60
10	CTCACCTCAA CCCCAGGCG GCCCCTCCAC AGGGCCCCCTC TCCTGCCTGG ACGGCTCTGC	120
	TGGTCTCCCC GTCCCCTGGA GAAGAACAAG GCC ATG GGT CGG CCC CTG CTG CTG	174
	Met Gly Arg Pro Leu Leu Leu	
	-19 -15	
15	CCC CTA CTG CCC CTG CTG CTG CCG CCA GCA TTT CTG CAG CCT AGT GGC	222
	Pro Leu Leu Pro Leu Leu Leu Pro Ala Phe Leu Gln Pro Ser Gly	
	-10 -5 1	
20	TCC ACA GGA TCT GGT CCA AGC TAC CTT TAT GGG GTC ACT CAA CCA AAA	270
	Ser Thr Gly Ser Gly Pro Ser Tyr Leu Tyr Gly Val Thr Gln Pro Lys	
	5 10 15 20	
25	CAC CTC TCA GCC TCC ATG GGT GGC TCT GTG GAA ATC CCC TTC TCC TTC	318
	His Leu Ser Ala Ser Met Gly Gly Ser Val Glu Ile Pro Phe Ser Phe	
	25 30 35	
30	TAT TAC CCC TGG GAG TTA GCC ACA GCT CCC GAC GTG AGA ATA TCC TGG	366
	Tyr Tyr Pro Trp Glu Leu Ala Thr Ala Pro Asp Val Arg Ile Ser Trp	
	40 45 50	
35	AGA CGG GGC CAC TTC CAC GGG CAG TCC TTC TAC AGC ACA AGG CCG CCT	414
	Arg Arg Gly His Phe His Gly Gln Ser Phe Tyr Ser Thr Arg Pro Pro	
	55 60 65	
40	TCC ATT CAC AAG GAT TAT GTG AAC CGG CTC TTT CTG AAC TGG ACA GAG	462
	Ser Ile His Lys Asp Tyr Val Asn Arg Leu Phe Leu Asn Trp Thr Glu	
	70 75 80	
45	GGT CAG AAG AGC GGC TTC CTC AGG ATC TCC AAC CTG CAG AAG CAG GAC	510
	Gly Gln Lys Ser Gly Phe Leu Arg Ile Ser Asn Leu Gln Lys Gln Asp	
	85 90 95 100	
50	CAG TCT GTG TAT TTC TGC CGA GTT GAG CTG GAC ACA CGG AGC TCA GGG	558
	Gln Ser Val Tyr Phe Cys Arg Val Glu Leu Asp Thr Arg Ser Ser Gly	
	105 110 115	
55	AGG CAG CAG TGG CAG TCC ATC GAG GGG ACC AAA CTC TCC ATC ACC CAG	606
	Arg Gln Gln Trp Gln Ser Ile Glu Gly Thr Lys Leu Ser Ile Thr Gln	
	120 125 130	
60	GCT GTC ACG ACC ACC ACC CAG AGG CCC AGC AGC ATG ACT ACC ACC TGG	654
	Ala Val Thr Thr Thr Thr Gln Arg Pro Ser Ser Met Thr Thr Thr Trp	
	135 140 145	
65	AGG CTC AGT AGC ACA ACC ACC ACA ACC GGC CTC AGG GTC ACA CAG GGC	702
	Arg Leu Ser Ser Thr Thr Thr Thr Thr Gly Leu Arg Val Thr Gln Gly	
	150 155 160	
70	AAA CGA CGC TCA GAC TCT TGG CAC ATA AGT CTG GAG ACT GCT GTG GGG	750

Lys Arg Arg Ser Asp Ser Trp His Ile Ser Leu Glu Thr Ala Val Gly
 165 170 175 180
 5 GTG GCA GTG GCT GTC ACT GTG CTC GGA ATC ATG ATT TTG GGA CTG ATC 798
 Val Ala Val Ala Val Thr Val Leu Gly Ile Met Ile Leu Gly Leu Ile
 185 190 195
 10 TGC CTC CTC AGG TGG AGG AGA AGG AAA GGT CAG CAG CGG ACT AAA GCC 846
 Cys Leu Leu Arg Trp Arg Arg Arg Lys Gly Gln Gln Arg Thr Lys Ala
 200 205 210
 15 ACA ACC CCA GCC AGG GAA CCC TTC CAA AAC ACA GAG GAG CCA TAT GAG 894
 Thr Thr Pro Ala Arg Glu Pro Phe Gln Asn Thr Glu Glu Pro Tyr Glu
 215 220 225
 20 AAT ATC AGG AAT GAA GGA CAA AAT ACA GAT CCC AAG CTA AAT CCC AAG 942
 Asn Ile Arg Asn Glu Gly Gln Asn Thr Asp Pro Lys Leu Asn Pro Lys
 230 235 240
 25 GAT GAC GGC ATC GTA TAT GCT TCC CTT GCC CTC TCC AGC TCC ACC TCA 990
 Asp Asp Gly Ile Val Tyr Ala Ser Leu Ala Leu Ser Ser Ser Thr Ser
 245 250 255 260
 30 CCC AGA GCA CCT CCC AGC CAC CGT CCC CTC AAG AGC CCC CAG AAC GAG 1038
 Pro Arg Ala Pro Pro Ser His Arg Pro Leu Lys Ser Pro Gln Asn Glu
 265 270 275
 35 ACC CTG TAC TCT GTC TTA AAG GCC TAACCAATGG ACAGCCCTCT CAAGACTGAA 1092
 Thr Leu Tyr Ser Val Leu Lys Ala
 280
 40 TGGTGAGGCC AGGTACAGTG GCGCACACCT GTAATCCCAG CTACTCTGAA GCCTGAGGCA 1152
 GAATCAAGTG AGCCCAGGAG TTCAGGGCCA GCTTTGATAA TGGAGCGAGA TGCCATCTCT 1212
 45 AGTTAAAAAT ATATATTAAC AATAAAGTAA CAAATTT 1249

(2) INFORMATION FOR SEQ ID NO:2:

40

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 303 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

45

- (ii) MOLECULE TYPE: protein

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

50

Met Gly Arg Pro Leu Leu Leu Pro Leu Leu Pro Leu Leu Leu Pro Pro
 -19 -15 -10 -5

Ala Phe Leu Gln Pro Ser Gly Ser Thr Gly Ser Gly Pro Ser Tyr Leu
 1 5 10

55

Tyr Gly Val Thr Gln Pro Lys His Leu Ser Ala Ser Met Gly Gly Ser
 15 20 25

Val Glu Ile Pro Phe Ser Phe Tyr Tyr Pro Trp Glu Leu Ala Thr Ala
 60

	30		35		40		45									
	Pro	Asp	Val	Arg	Ile	Ser	Trp	Arg	Arg	Gly	His	Phe	His	Gly	Gln	Ser
					50					55					60	
5	Phe	Tyr	Ser	Thr	Arg	Pro	Pro	Ser	Ile	His	Lys	Asp	Tyr	Val	Asn	Arg
				65					0					75		
10	Leu	Phe	Leu	Asn	Trp	Thr	Glu	Gly	Ile	Lys	Ser	Gly	Phe	Leu	Arg	Ile
			80					85					90			
	Ser	Asn	Leu	Gln	Lys	Gln	Asp	Gly	Ser	Val	Tyr	Phe	Cys	Arg	Val	Glu
		95					100					105				
15	Leu	Asp	Thr	Arg	Ser	Ser	Gly	Arg	Gln	Gln	Trp	Gln	Ser	Ile	Glu	Gly
	110					115					120				125	
	Thr	Lys	Leu	Ser	Ile	Thr	Gln	Ala	Val	Thr	Thr	Thr	Thr	Gln	Arg	Pro
					130					135					140	
20	Ser	Ser	Met	Thr	Thr	Thr	Trp	Arg	Leu	Ser	Ser	Thr	Thr	Thr	Thr	Thr
				145					150					155		
25	Gly	Leu	Arg	Val	Thr	Gln	Gly	Lys	Arg	Arg	Ser	Asp	Ser	Trp	His	Ile
			160					165					170			
	Ser	Leu	Glu	Thr	Ala	Val	Gly	Val	Ala	Val	Ala	Val	Thr	Val	Leu	Gly
		175					180					185				
30	Ile	Met	Ile	Leu	Gly	Leu	Ile	Cys	Leu	Leu	Arg	Trp	Arg	Arg	Arg	Lys
	190					195					200					205
	Gly	Gln	Gln	Arg	Thr	Lys	Ala	Thr	Thr	Pro	Ala	Arg	Glu	Pro	Phe	Gln
					210					215					220	
35	Asn	Thr	Glu	Glu	Pro	Tyr	Glu	Asn	Ile	Arg	Asn	Glu	Gly	Gln	Asn	Thr
				225					230					235		
	Asp	Pro	Lys	Leu	Asn	Pro	Lys	Asp	Asp	Gly	Ile	Val	Tyr	Ala	Ser	Leu
40			240					245					250			
	Ala	Leu	Ser	Ser	Ser	Thr	Ser	Pro	Arg	Ala	Pro	Pro	Ser	His	Arg	Pro
		255					260					265				
45	Leu	Lys	Ser	Pro	Gln	Asn	Glu	Thr	Leu	Tyr	Ser	Val	Leu	Lys	Ala	
	270					275				280						

(2) INFORMATION FOR SEQ ID NO:3:

- 50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 376 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

55 (ii) MOLECULE TYPE: cDNA

ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 78..374

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

	CCCCAGTGTC CCTAGACAGA GCATCCTTGC CTTCTGATG GCTTTGCTGA TCTCGCTTCC	60
	CTGGAGGGAC TCCAGCC ATG GCT CAG GTC CTG CTT CTG CTC TCA TCA GGC	110
10	Met Ala Gln Val Leu Leu Leu Ser Ser Gly	
	1 5 10	
	TGT CTG CAT GCT GGA AAT TCA GAA AGA TAC AAC AGA AAA AAT GGC TTT	158
	Cys Leu His Ala Gly Asn Ser Glu Arg Tyr Asn Arg Lys Asn Gly Phe	
15	15 20 25	
	GGG GTC AAC CAA CCT GAA CGC TGC TCT GGA GTC CAG GGT GGC TCC ATC	206
	Gly Val Asn Gln Pro Glu Arg Cys Ser Gly Val Gln Gly Gly Ser Ile	
	30 35 40	
20	GAC ATC CCC TTC TCC TTC TAT TTC CCC TGG AAG TTG GCC AAG GAT CCA	254
	Asp Ile Pro Phe Ser Phe Tyr Phe Pro Trp Lys Leu Ala Lys Asp Pro	
	45 50 55	
25	CAG ATG AGC ATA GCC TGG AAA TGG AAG GAT TTC CAT GGG GAA GTC ATC	302
	Gln Met Ser Ile Ala Trp Lys Trp Lys Asp Phe His Gly Glu Val Ile	
	60 65 70 75	
	TAC AAC TCC TCC CTG CCT TTC ATA CAT GAG CAC TTC AAG GGC CGG CTC	350
30	Tyr Asn Ser Ser Leu Pro Phe Ile His Glu His Phe Lys Gly Arg Leu	
	80 85 90	
	ATC CTG AAC TGG ACA CAG GGT CAG AC	376
35	Ile Leu Asn Trp Thr Gln Gly Gln	
	95	

(2) INFORMATION FOR SEQ ID NO:4:

40 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 99 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

50	Met Ala Gln Val Leu Leu Leu Leu Ser Ser Gly Cys Leu His Ala Gly	
	1 5 10 15	
	Asn Ser Glu Arg Tyr Asn Arg Lys Asn Gly Phe Gly Val Asn Gln Pro	
	20 25 30	
55	Glu Arg Cys Ser Gly Val Gln Gly Gly Ser Ile Asp Ile Pro Phe Ser	
	35 40 45	
	Phe Tyr Phe Pro Trp Lys Leu Ala Lys Asp Pro Gln Met Ser Ile Ala	
	50 55 60	

Trp Lys Trp Lys Asp Phe His Gly Glu Val Ile Tyr Asn Ser Ser Leu
65 70 75 80

5 Pro Phe Ile His Glu His Phe Lys Gly Arg Leu Ile Leu Asn Trp Thr
85 90 95

Gln Gly Gln

10

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1279 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
(B) LOCATION: 155..1015

25

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
(B) LOCATION: 1247

30

(D) OTHER INFORMATION: /note= Y at nucleotide 1247 may be C or T

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
(B) LOCATION: 218..1015

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ACCGGTCCGG AATTCCCGGG TCGACCCACG CGTCCGGGAA GCCCCATAGG CAGGAGGCCCC 60

40 CCGGGCAGCA CATCCTGTCT GCTTGTGTCT GCTGCAGAGT TCTGTCCTTG CATTGGTGCG 120

CCTCAGGCCA GGCTGCACTG CTGGGACCTG GGCC ATG TCT CCC CAC CCC ACC 172

Met Ser Pro His Pro Thr
-21 -20

45 GCC CTC CTG GGC CTA GTG CTC TGC CTG GCC CAG ACC ATC CAC ACG CAG 220
Ala Leu Leu Gly Leu Val Leu Cys Leu Ala Gln Thr Ile His Thr Gln
-15 -10 -5 1

50 GAG GAA GAT CTG CCC AGA CCC TCC ATC TCG GCT GAG CCA GGC ACC GTG 268
Glu Glu Asp Leu Pro Arg Pro Ser Ile Ser Ala Glu Pro Gly Thr Val
5 10 15

55 ATC CCC CTG GGG AGC CAT GTG ACT TTC GTG TGC CGG GGC CCG GTT GGG 316
Ile Pro Leu Gly Ser His Val Thr Phe Val Cys Arg Gly Pro Val Gly
20 25 30

GTT CAA ACA TTC CGC CTG GAG AGG GAG AGT AGA TCC ACA TAC AAT GAT 364
Val Gln Thr Phe Arg Leu Glu Arg Glu Ser Arg Ser Thr Tyr Asn Asp

	35	40	45	
5	ACT GAA GAT GTG TCT CAA GCT AGT CCA TCT GAG TCA GAG GCC AGA TTC Thr Glu Asp Val Ser Gln Ala Ser Pro Ser Glu Ser Glu Ala Arg Phe 50 55 60 65	412		
10	CGC ATT GAC TCA GTA AGT GAA GGA AAT GCC GGG CCT TAT CGC TGC ATC Arg Ile Asp Ser Val Ser Glu Gly Asn Ala Gly Pro Tyr Arg Cys Ile 70 75 80	460		
15	TAT TAT AAG CCC CCT AAA TGG TCT GAG CAG AGT GAC TAC CTG GAG CTG Tyr Tyr Lys Pro Pro Lys Trp Ser Glu Gln Ser Asp Tyr Leu Glu Leu 85 90 95	508		
20	CTG GTG AAA GAA ACC TCT GGA GGC CCG GAC TCC CCG GAC ACA GAG CCC Leu Val Lys Glu Thr Ser Gly Gly Pro Asp Ser Pro Asp Thr Glu Pro 100 105 110	556		
25	GGC TCC TCA GCT GGA CCC ACG CAG AGG CCG TCG GAC AAC AGT CAC AAT Gly Ser Ser Ala Gly Pro Thr Gln Arg Pro Ser Asp Asn Ser His Asn 115 120 125	604		
30	GAG CAT GCA CCT GCT TCC CAA GGC CTG AAA GCT GAG CAT CTG TAT ATT Glu His Ala Pro Ala Ser Gln Gly Leu Lys Ala Glu His Leu Tyr Ile 130 135 140 145	652		
35	CTC ATC GGG GTC TCA GTG GTC TTC CTC TTC TGT CTC CTC CTC CTG GTC Leu Ile Gly Val Ser Val Val Phe Leu Phe Cys Leu Leu Leu Val 150 155 160	700		
40	CTC TTC TGC CTC CAT CGC CAG AAT CAG ATA AAG CAG GGG CCC CCC AGA Leu Phe Cys Leu His Arg Gln Asn Gln Ile Lys Gln Gly Pro Pro Arg 165 170 175	748		
45	AGC AAG GAC GAG GAG CAG AAG CCA CAG CAG AGG CCT GAC CTG GCT GTT Ser Lys Asp Glu Glu Gln Lys Pro Gln Gln Arg Pro Asp Leu Ala Val 180 185 190	796		
50	GAT GTT CTA GAG AGG ACA GCA GAC AAG GCC ACA GTC AAT GGA CTT CCT Asp Val Leu Glu Arg Thr Ala Asp Lys Ala Thr Val Asn Gly Leu Pro 195 200 205	844		
55	GAG AAG GAC AGA GAG ACG GAC ACC TCG GCC CTG GCT GCA GGG AGT TCC Glu Lys Asp Arg Glu Thr Asp Thr Ser Ala Leu Ala Ala Gly Ser Ser 210 215 220 225	892		
60	CAG GAG GTG ACG TAT GCT CAG CTG GAC CAC TGG GCC CTC ACA CAG AGG Gln Glu Val Thr Tyr Ala Gln Leu Asp His Trp Ala Leu Thr Gln Arg 230 235 240	940		
65	ACA GCC CGG GCT GTG TCC CCA CAG TCC ACA AAG CCC ATG GCC GAG TCC Thr Ala Arg Ala Val Ser Pro Gln Ser Thr Lys Pro Met Ala Glu Ser 245 250 255	988		
70	ATC ACG TAT GCA GCC GTT GCC AGA CAC TGACCCCATATA CCCACCTGGC Ile Thr Tyr Ala Ala Val Ala Arg His 260 265	1035		
75	CTCTGCACCT GAGGGTAGAA AGTCACTCTA GGAAAAGCCT GAAGCAGCCA TTTGGAAGGC 64	1095		

TTCCTGTTGG ATTCCTCTTC ATCTAGAAAAG CCAGCCAGGC AGCTGTCCTG GAGACAAGAG 1155
 CTGGAGACTG GAGGTTTCTA ACCAGCATCC AGAAGGTTTC TTAGCCAGGT GGTCCCTTCT 1215
 ACAATCGGAC AGCTCCTTGG ACAGACTGTT TYTCAGTTAT TTCCAAAAAC CCAGCTACAG 1275
 TTCC 1279

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 287 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ser Pro His Pro Thr Ala Leu Leu Gly Leu Val Leu Cys Leu Ala
 -21 -20 -15 -10
 Gln Thr Ile His Thr Gln Glu Glu Asp Leu Pro Arg Pro Ser Ile Ser
 -5 1 5 10
 Ala Glu Pro Gly Thr Val Ile Pro Leu Gly Ser His Val Thr Phe Val
 15 20 25
 Cys Arg Gly Pro Val Gly Val Gln Thr Phe Arg Leu Glu Arg Glu Ser
 30 35 40
 Arg Ser Thr Tyr Asn Asp Thr Glu Asp Val Ser Gln Ala Ser Pro Ser
 45 50 55
 Glu Ser Glu Ala Arg Phe Arg Ile Asp Ser Val Ser Glu Gly Asn Ala
 60 65 70 75
 Gly Pro Tyr Arg Cys Ile Tyr Tyr Lys Pro Pro Lys Trp Ser Glu Gln
 80 85 90
 Ser Asp Tyr Leu Glu Leu Leu Val Lys Glu Thr Ser Gly Gly Pro Asp
 95 100 105
 Ser Pro Asp Thr Glu Pro Gly Ser Ser Ala Gly Pro Thr Gln Arg Pro
 110 115 120
 Ser Asp Asn Ser His Asn Glu His Ala Pro Ala Ser Gln Gly Leu Lys
 125 130 135
 Ala Glu His Leu Tyr Ile Leu Ile Gly Val Ser Val Val Phe Leu Phe
 140 145 150 155
 Cys Leu Leu Leu Leu Val Leu Phe Cys Leu His Arg Gln Asn Gln Ile
 160 165 170
 Lys Gln Gly Pro Pro Arg Ser Lys Asp Glu Glu Gln Lys Pro Gln Gln
 175 180 185

65

Arg Pro Asp Leu Ala Val Asp Val Leu Glu Arg Thr Ala Asp Lys Ala
 190 195 200
 5 Thr Val Asn Gly Leu Pro Glu Lys Asp Arg Glu Thr Asp Thr Ser Ala
 205 210 215
 Leu Ala Ala Gly Ser Ser Gln Glu Val Thr Tyr Ala Gln Leu Asp His
 220 225 230 235
 10 Trp Ala Leu Thr Gln Arg Thr Ala Arg Ala Val Ser Pro Gln Ser Thr
 240 245 250
 Lys Pro Met Ala Glu Ser Ile Thr Tyr Ala Ala Val Ala Arg His
 15 255 260 265

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1728 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 69..929

(ix) FEATURE:
 (A) NAME/KEY: mat_peptide
 (B) LOCATION: 132..929

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AAAGGCTGCA GAGTTCTGTC CTTGCATTGG TGCGCCTCAG GCCAGGCTGC .CTGCTGGGA 60
 40 CCTGGGGCC ATG TCT CCC CAC CCC ACC GCC CTC CTG GGC CTA CCG CTC TGC 110
 Met Ser Pro His Pro Thr Ala Leu Leu Gly Leu Val Leu Cys
 -21 -20 -15 -10
 45 CTG GCC CAG ACC ATC CAC ACG CAG GAG GAA GAT CTG CCC AGA CCC TCC 158
 Leu Ala Gln Thr Ile His Thr Gln Glu Glu Asp Leu Pro Arg Pro Ser
 -5 1 5
 50 ATC TCG GCT GAG CCA GGC ACC GTG ATC CCC CTG GGG ACC CAT GTG ACT 206
 Ile Ser Ala Glu Pro Gly Thr Val Ile Pro Leu Gly Ser His Val Thr
 10 15 20 25
 55 TTC GTG TGC CGG GGC CCG GTT GGG GTT CAA ACA TTC CGC CTG GAG AGG 254
 Phe Val Cys Arg Gly Pro Val Gly Val Gln Thr Phe Arg Leu Glu Arg
 30 35 40
 GAG AGT AGA TCC ACA TAC AAT GAT ACT GAA GAT G G TCT CAA GCT AGT 302
 Glu Ser Arg Ser Thr Tyr Asn Asp Thr Glu Asp Val Ser Gln Ala Ser
 45 50 55
 66

5	CCA TCT GAG TCA GAG GCC AGA TTC CGC ATT GAC TCA GTA AGT GAA GGA	350
	Pro Ser Glu Ser Glu Ala Arg Phe Arg Ile Asp Ser Val Ser Glu Gly	
	60 65 70	
10	AAT GCC GGG CCT TAT CGC TGC ATC TAT TAT AAG CCC CCT AAA TGG TCT	398
	Asn Ala Gly Pro Tyr Arg Cys Ile Tyr Tyr Lys Pro Pro Lys Trp Ser	
	75 80 85	
15	GAG CAG AGT GAC TAC CTG GAG CTG CTG GTG AAA GAA ACC TCT GGA GGC	446
	Glu Gln Ser Asp Tyr Leu Glu Leu Leu Val Lys Glu Thr Ser Gly Gly	
	90 95 100 105	
20	CCG GAC TCC CCG GAC ACA GAG CCC GGC TCC TCA GCT GGA CCC ACG CAG	494
	Pro Asp Ser Pro Asp Thr Glu Pro Gly Ser Ser Ala Gly Pro Thr Gln	
	110 115 120	
25	AGG CCG TCG GAC AAC AGT CAC AAT GAG CAT GCA CCT GCT TCC CAA GGC	542
	Arg Pro Ser Asp Asn Ser His Asn Glu His Ala Pro Ala Ser Gln Gly	
	125 130 135	
30	CTG AAA GCT GAG CAT CTG TAT ATT CTC ATC GGG GTC TCA GTG GTC TTC	590
	Leu Lys Ala Glu His Leu Tyr Ile Leu Ile Gly Val Ser Val Val Phe	
	140 145 150	
35	CTC TTC TGT CTC CTC CTC CTG GTC CTC TTC TGC CTC CAT CGC CAG AAT	638
	Leu Phe Cys Leu Leu Leu Leu Val Leu Phe Cys Leu His Arg Gln Asn	
	155 160 165	
40	CAG ATA AAG CAG GGG CCC CCC AGA AGC AAG GAC GAG GAG CAG AAG CCA	686
	Gln Ile Lys Gln Gly Pro Pro Arg Ser Lys Asp Glu Glu Gln Lys Pro	
	170 175 180 185	
45	CAG CAG AGG CCT GAC CTG GCT GTT GAT GTT CTA GAG AGG ACA GCA GAC	734
	Gln Gln Arg Pro Asp Leu Ala Val Asp Val Leu Glu Arg Thr Ala Asp	
	190 195 200	
50	AAG GCC ACA GTC AAT GGA CTT CCT GAG AAG GAC AGA GAG ACG GAC ACC	782
	Lys Ala Thr Val Asn Gly Leu Pro Glu Lys Asp Arg Glu Thr Asp Thr	
	205 210 215	
55	TCG GCC CTG GCT GCA GGG AGT TCC CAG GAG GTG ACG TAT GCT CAG CTG	830
	Ser Ala Leu Ala Ala Gly Ser Ser Gln Glu Val Thr Tyr Ala Gln Leu	
	220 225 230	
60	GAC CAC TGG GCC CTC ACA CAG AGG ACA GCC CGG GCT GTG TCC CCA CAG	878
	Asp His Trp Ala Leu Thr Gln Arg Thr Ala Arg Ala Val Ser Pro Gln	
	235 240 245	
65	TCC ACA AAG CCC ATG GCC GAG TCC ATC ACG TAT GCA GCC GTT GCC AGA	926
	Ser Thr Lys Pro Met Ala Glu Ser Ile Thr Tyr Ala Ala Val Ala Arg	
	250 255 260 265	
70	CAC TGACCCATA CCCACCTGGC CTCTGCACCT GAGGGTAGAA AGTCACTCTA	979
	His	
	GGAAAAGCCT GAAGCAGCCA TTTGGAAGGC TTCCTGTTGG ATTCCTCTTC ATCTAGAAAG	1039

CCAGCCAGGC AGCTGTCCTG GAGACAAGAG CTGGAGACTG GAGGTTTCTA ACCAGCATCC 1099
 AGAAGGTTTCG TTAGCCAGGT GGTCCCTTCT ACAATCGAGC AGCTCCTTGG ACAGACTGTT 1159
 5 TCTCAGTTAT TTCCAGAGAC CCAGCTACAG TTCCCTGGCT GTTCTAGAG ACCCAGCTTT 1219
 ATTCACCTGA CTGTTTCCAG AGACCCAGCT AAAGTCACCT GCCTGTTCTA AAGGCCCAGC 1279
 TACAGCCAAT CAGCCGATTT CCTGAGCACT GATGCCACCT CCAAGCTTGT CCTAGGTGTC 1339
 10 TGCTGTGAAC CTCCAGTGAC CCCAGAGACT TTGCTGTAAT TATCTGCCCT GCTGACCCTA 1399
 AAGACCTTCC TAGAAGTCAA GAGCTAGCCT TGAGACTGTG CTATACACAC ACAGCTGAGA 1459
 15 GCCAAGCCCA GTTCTCTGGG TTGTGCTTTA CTCCACGCAT CAATAAATAA TTTTGAAGGC 1519
 CTCACATCTG GCAGCCCCAG GCCTGGTCCT GGGTGCATAG GTCTCTCGGA CCCACTCTCT 1579
 GCCTTCACAG TTGTTCAAAG CTGAGTGAGG GAAACAGGAC TTACGAAAAC GTGTCAGCGT 1639
 20 TTTCTTTTAA AAATTTAATT GATCAGGATT GTACGTAAAA AAAAAAAAAA AAAAAAAAAA 1699
 AAAAAAAAAA AAAAAAAAAA AAAAAAAGG 1728

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 287 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ser Pro His Pro Thr Ala Leu Leu Gly Leu Val Leu Cys Leu Ala
 -21 -20 -15 -10
 40 Gln Thr Ile His Thr Gln Glu Glu Asp Leu Pro Arg Pro Ser Ile Ser
 -5 1 5 10
 Ala Glu Pro Gly Thr Val Ile Pro Leu Gly Ser His Val Thr Phe Val
 15 20 25
 45 Cys Arg Gly Pro Val Gly Val Gln Thr Phe Arg Leu Glu Arg Glu Ser
 30 35 40
 50 Arg Ser Thr Tyr Asn Asp Thr Glu Asp Val Ser Gln Ala Ser Pro Ser
 45 50 55
 Glu Ser Glu Ala Arg Phe Arg Ile Asp Ser Val Ser Glu Gly Asn Ala
 60 65 70 75
 55 Gly Pro Tyr Arg Cys Ile Tyr Tyr Lys Pro Pro Lys Trp Ser Glu Gln
 80 85 90
 Ser Asp Tyr Leu Glu Leu Leu Val Lys Glu Thr Ser Gly Gly Pro Asp
 95 100 105

5 Ser Pro Asp Thr Glu Pro Gly Ser Ser Ala Gly Pro Thr Gln Arg Pro
 110 115 120
 10 Ala Glu His Leu Tyr Ile Leu Ile Gly Val Ser Val Val Phe Leu Phe
 140 145 150 155
 15 Cys Leu Leu Leu Leu Val Leu Phe Cys Leu His Arg Gln Asn Gln Ile
 160 165 170
 20 Lys Gln Gly Pro Pro Arg Ser Lys Asp Glu Glu Gln Lys Pro Gln Gln
 175 180 185
 25 Arg Pro Asp Leu Ala Val Asp Val Leu Glu Arg Thr Ala Asp Lys Ala
 190 195 200
 30 Thr Val Asn Gly Leu Pro Glu Lys Asp Arg Glu Thr Asp Thr Ser Ala
 205 210 215
 35 Leu Ala Ala Gly Ser Ser Gln Glu Val Thr Tyr Ala Gln Leu Asp His
 220 225 230 235
 40 Trp Ala Leu Thr Gln Arg Thr Ala Arg Ala Val Ser Pro Gln Ser Thr
 240 245 250
 45 Lys Pro Met Ala Glu Ser Ile Thr Tyr Ala Ala Val Ala Arg His
 255 260 265

(2) INFORMATION FOR SEQ ID NO:9:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 568 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: cDNA

45 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 24..428

50 (ix) FEATURE:
 (A) NAME/KEY: mat_peptide
 (B) LOCATION: 87..428

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

55 CCACGCGTCC GGGGACCGGG GCC ATG TCT CCA CAC CTC ACT GCT CTC CTG 50
 Met Ser Pro His Leu Thr Ala Leu Leu
 -21 -20 -15
 GGC CTA GTG CTC TGC CTG GCC CAG ACC ATC CAC ACG CAG GAG GGG GCC 98
 Gly Leu Val Leu Cys Leu Ala Gln Thr Ile His Thr Gln Glu Gly Ala

	-10	-5	1	
5	CTT CCC AGA CCC TCC ATC TCG GCT GAG CCA GGC ACT GTG ATC TCC CCG Leu Pro Arg Pro Ser Ile Ser Ala Glu Pro Gly Thr Val Ile Ser Pro 5 10 15 20			146
10	GGG AGC CAT GTG ACT TTC ATG TGC CGG GGC CCG GTT GGG GTT CAA ACA Gly Ser His Val Thr Phe Met Cys Arg Gly Pro Val Gly Val Gln Thr 25 30 35			194
15	TTC CGC CTG GAG AGG GAG GAT AGA GCC AAG TAC AAA GAT AGT TAT AAT Phe Arg Leu Glu Arg Glu Asp Arg Ala Lys Tyr Lys Asp Ser Tyr Asn 40 45 50			242
20	GTG TTT CGA CTT GGT CCA TCT GAG TCA GAG GCC AGA TTC CAC ATT GAC Val Phe Arg Leu Gly Pro Ser Glu Ser Glu Ala Arg Phe His Ile Asp 55 60 65			290
25	TCA GTA AGT GAA GGA AAT GCC GGG CTT TAT CGC TGC CTC TAT TAT AAG Ser Val Ser Glu Gly Asn Ala Gly Leu Tyr Arg Cys Leu Tyr Tyr Lys 70 75 80			338
30	CCC CCT GGA TGG TCT GAG CAC AGT GAC TTC CTG GAG CTG CTG GTG AAA Pro Pro Gly Trp Ser Glu His Ser Asp Phe Leu Glu Leu Leu Val Lys 85 90 95 100			386
35	GGG ACT GTG CCA GGC ACT GAA GCC TCC GGA TTT GAT GCA CCA Gly Thr Val Pro Gly Thr Glu Ala Ser Gly Phe Asp Ala Pro 105 110			428
40	TGAATGAGGA GAAATGGCCT CCCGTCTTGT GAACTTCAAT GGGGAGAAAT AATTAGAATG			488
45	AGCAATAGAA ATGCACAGAT GCCTATACAT ACATATACAA ATAAAAAGAT ACGATTTCGA			548
50	AAAAAAAAAA AAAAAAGGGC			568

(2) INFORMATION FOR SEQ ID NO:10:

40 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 135 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

50	Met Ser Pro His Leu Thr Ala Leu Leu Gly Leu Val Leu Cys Leu Ala -21 -20 -15 -10
55	Gln Thr Ile His Thr Gln Glu Gly Ala Leu Pro Arg Pro Ser Ile Ser -5 1 5 10
	Ala Glu Pro Gly Thr Val Ile Ser Pro Gly Ser His Val Thr Phe Met 15 20 25
	Cys Arg Gly Pro Val Gly Val Gln Thr Phe Arg Leu Glu Arg Glu Asp 30 35 40

70

Arg Ala Lys Tyr Lys Asp Ser Tyr Asn Val Phe Arg Leu Gly Pro Ser
45 50 55

5 Glu Ser Glu Ala Arg Phe His Ile Asp Ser Val Ser Glu Gly Asn Ala
60 65 70 75

Gly Leu Tyr Arg Cys Leu Tyr Tyr Lys Pro Pro Gly Trp Ser Glu His
80 85 90

10 Ser Asp Phe Leu Glu Leu Leu Val Lys Gly Thr Val Pro Gly Thr Glu
95 100 105

15 Ala Ser Gly Phe Asp Ala Pro
110

(2) INFORMATION FOR SEQ ID NO:11:

20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1620 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
30 (A) NAME/KEY: CDS
(B) LOCATION: 81..1397

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

35 GTCGACCCAC GCGTCCGCCT CTGTCCTGCC AGCACCGAGG GCTCATCCAT CCACAGAGCA 60
GTGCAGTGGG AGGAGACGCC ATG ACC CCC ATC CTC ACG GTC CTG ATC TGT 110
Met Thr Pro Ile Leu Thr Val Leu Ile Cys
1 5 10
40 CTC GGG CTG AGC CTG GAC CCC AGG ACC CAC GTG CAG GCA GGG CCC CTC 158
Leu Gly Leu Ser Leu Asp Pro Arg Thr His Val Gln Ala Gly Pro Leu
15 20 25
45 CCC AAG CCC ACC CTC TGG GCT GAG CCA GGC TCT GTG ATC ACC CAA GGG 206
Pro Lys Pro Thr Leu Trp Ala Glu Pro Gly Ser Val Ile Thr Gln Gly
30 35 40
50 AGT CCT GTG ACC CTC AGG TGT CAG GGG AGC CTG GAG ACG CAG GAG TAC 254
Ser Pro Val Thr Leu Arg Cys Gln Gly Ser Leu Glu Thr Gln Glu Tyr
45 50 55
55 CAT CTA TAT AGA GAA AAG AAA ACA GCA CTC TGG ATT ACA CGG ATC CCA 302
His Leu Tyr Arg Glu Lys Lys Thr Ala Leu Trp Ile Thr Arg Ile Pro
60 65 70
CAG GAG CTT GTG AAG AAG GGC CAG TTC CCC ATC CTA TCC ATC ACC TGG 350
Gln Glu Leu Val Lys Lys Gly Gln Phe Pro Ile Leu Ser Ile Thr Trp
75 80 85 90

	GAA CAT GCA GGG CGG TAT TGC TGT ATC TAT GGC AGC CAC ACT GCA GGC Glu His Ala Gly Arg Tyr Cys Cys Ile Tyr Gly Ser His Thr Ala Gly 95 100 105	398
5	CTC TCA GAG AGC AGT GAC CCC CTG GAG CTG GTG GTG ACA GGA GCC TAC Leu Ser Glu Ser Ser Asp Pro Leu Glu Leu Val Val Thr Gly Ala Tyr 110 115 120	446
10	AGC AAA CCC ACC CTC TCA GCT CTG CCC AGC CCT GTG GTG ACC TCA GGA Ser Lys Pro Thr Leu Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly 125 130 135	494
15	GGG AAT GTG ACC ATC CAG TGT GAC TCA CAG GTG GCA TTT GAT GGC TTC Gly Asn Val Thr Ile Gln Cys Asp Ser Gln Val Ala Phe Asp Gly Phe 140 145 150	542
20	ATT CTG TGT AAG GAA GGA GAA GAT GAA CAC CCA CAA TGC CTG AAC TCC Ile Leu Cys Lys Glu Gly Glu Asp Glu His Pro Gln Cys Leu Asn Ser 155 160 165 170	590
	CAT TCC CAT GCC CGT GGG TCA TCC CGG GCC ATC TTC TCC GTG GGC CCC His Ser His Ala Arg Gly Ser Ser Arg Ala Ile Phe Ser Val Gly Pro 175 180 185	638
25	GTG AGC CCA AGT CGC AGG TGG TCG TAC AGG TGC TAT GGT TAT GAC TCG Val Ser Pro Ser Arg Arg Trp Ser Tyr Arg Cys Tyr Gly Tyr Asp Ser 190 195 200	686
30	CGC GCT CCC TAT GTG TGG TCT CTA CCC AGT GAT CTC CTG GGG CTC CTG Arg Ala Pro Tyr Val Trp Ser Leu Pro Ser Asp Leu Leu Gly Leu Leu 205 210 215	734
35	GTC CCA GGT GTT TCT AAG AAG CCA TCA CTC TCA GTG CAG CCG GGT CCT Val Pro Gly Val Ser Lys Lys Pro Ser Leu Ser Val Gln Pro Gly Pro 220 225 230	782
40	GTC GTG GCC CCT GGG GAG AAG CTG ACC TTC CAG TGT GGC TCT GAT GCC Val Val Ala Pro Gly Glu Lys Leu Thr Phe Gln Cys Gly Ser Asp Ala 235 240 245 250	830
	GGC TAC GAC AGA TTT GTT CTG TAC AAG GAG TGG GGA CGT GAC TTC CTC Gly Tyr Asp Arg Phe Val Leu Tyr Lys Glu Trp Gly Arg Asp Phe Leu 255 260 265	878
45	CAG CGC CCT GGC CGG CAG CCC CAG GCT GGG CTC TCC CAG GCC AAC TTC Gln Arg Pro Gly Arg Gln Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe 270 275 280	926
50	ACC CTG GGC CCT GTG AGC CGC TCC TAC GGG GGC CAG TAC ACA TGC TCC Thr Leu Gly Pro Val Ser Arg Ser Tyr Gly Gly Gln Tyr Thr Cys Ser 285 290 295	974
55	GGT GCA TAC AAC CTC TCC TCC GAG TGG TCG GCC CCC AGC GAC CCC CTG Gly Ala Tyr Asn Leu Ser Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu 300 305 310	1022
	GAC ATC CTG ATC ACA GGA CAG ATC CGT GCC AGA CCC TTC CTC TCC GTG Asp Ile Leu Ile Thr Gly Gln Ile Arg Ala Arg Pro Phe Leu Ser Val 72	1070

	315		320		325		330	
5	CGG CCG GGC CCC ACA GTG GCC TCA GGA GAG AAC GTG ACC CTG CTG TGT							1118
	Arg Pro Gly Pro Thr Val Ala Ser Gly Glu Asn Val Thr Leu Leu Cys							
		335			340		345	
10	CAG TCA CAG GGA GGG ATG CAC ACT TTC CTT TTG ACC AAG GAG GGG GCA							1166
	Gln Ser Gln Gly Gly Met His Thr Phe Leu Leu Thr Lys Glu Gly Ala							
		350			355		360	
15	GCT GAT TCC CCG CTG CGT CTA AAA TCA AAG CGC CAA TCT CAT AAG TAC							1214
	Ala Asp Ser Pro Leu Arg Leu Lys Ser Lys Arg Gln Ser His Lys Tyr							
		365			370		375	
20	CAG GCT GAA TTC CCC ATG AGT CCT GTG ACC TCG GCC CAC GCG GGG ACC							1262
	Gln Ala Glu Phe Pro Met Ser Pro Val Thr Ser Ala His Ala Gly Thr							
		380			385		390	
25	TAC AGG TGC TAC GGC TCA CTC AGC TCC AAC CCC TAC CTG CTG ACT CAC							1310
	Tyr Arg Cys Tyr Gly Ser Leu Ser Ser Asn Pro Tyr Leu Leu Thr His							
		395			400		405	410
30	CCC AGT GAC CCC CTG GAG CTC GTG GTC TCA GGA GCA GCT GAG ACC CTC							1358
	Pro Ser Asp Pro Leu Glu Leu Val Val Ser Gly Ala Ala Glu Thr Leu							
		415			420		425	
35	AGC CCA CCA CAA AAC AAG TCC GAC TCC AAG GCT GGT GAG TGAGGAGATG							1407
	Ser Pro Pro Gln Asn Lys Ser Asp Ser Lys Ala Gly Glu							
		430			435			
40	CTTGCCGTGA TGACGCTGGG CACAGAGGGT CAGGTCCTGT CAAGAGGAGC TGGGTGTCCT							1467
	GGGTGGACAT TTGAAGAATT ATATTCATTC CAACTTGAAG AATTATTCAA CACCTTTAAC							1527
45	AATGTATATG TGAAGTACTT TATTCTTTCA TATTTTAAAA ATAAAAGATA ATTATCCATG							1587
	AAAAAAAAA AAAAAAAAAA AAAGGGCGGC CGC							1620

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 439 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met	Thr	Pro	Ile	Leu	Thr	Val	Leu	Ile	Cys	Leu	Gly	Leu	Ser	Leu	Asp
1					5				10					15	

Pro	Arg	Thr	His	Val	Gln	Ala	Gly	Pro	Leu	Pro	Lys	Pro	Thr	Leu	Trp
			20					25					30		

Ala	Glu	Pro	Gly	Ser	Val	Ile	Thr	Gln	Gly	Ser	Pro	Val	Thr	Leu	Arg
	35						40					45			

Cys Gln Gly Ser Leu Glu Thr Gln Glu Tyr His Leu Tyr Arg Glu Lys
 50 55 60
 Lys Thr Ala Leu Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys
 65 70 75 80
 Gly Gln Phe Pro Ile Leu Ser Ile Thr Trp Glu His Ala Gly Arg Tyr
 85 90 95
 Cys Cys Ile Tyr Gly Ser His Thr Ala Gly Leu Ser Glu Ser Ser Asp
 100 105 110
 Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ser Lys Pro Thr Leu Ser
 115 120 125
 Ala Leu Pro Ser Pro Val Val Thr Ser Gly Gly Asn Val Thr Ile Gln
 130 135 140
 Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ile Leu Cys Lys Glu Gly
 145 150 155 160
 Glu Asp Glu His Pro Gln Cys Leu Asn Ser His Ser His Ala Arg Gly
 165 170 175
 Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg
 180 185 190
 Trp Ser Tyr Arg Cys Tyr Gly Tyr Asp Ser Arg Ala Pro Tyr Val Trp
 195 200 205
 Ser Leu Pro Ser Asp Leu Leu Gly Leu Leu Val Pro Gly Val Ser Lys
 210 215 220
 Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
 225 230 235 240
 Lys Leu Thr Phe Gln Cys Gly Ser Asp Ala Gly Tyr Asp Arg Phe Val
 245 250 255
 Leu Tyr Lys Glu Trp Gly Arg Asp Phe Leu Gln Arg Pro Gly Arg Gln
 260 265 270
 Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 275 280 285
 Arg Ser Tyr Gly Gly Gln Tyr Thr Cys Ser Gly Ala Tyr Asn Leu Ser
 290 295 300
 Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly
 305 310 315 320
 Gln Ile Arg Ala Arg Pro Phe Leu Ser Val Arg Pro Gly Pro Thr Val
 325 330 335
 Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Gln Gly Gly Met
 340 345 350
 His Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala Asp Ser Pro Leu Arg
 355 360 365

74

Leu Lys Ser Lys Arg Gln Ser His Lys Tyr Gln Ala Glu Phe Pro Met
 370 375 380

5 Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser
 385 390 395 400

10 Leu Ser Ser Asn Pro Tyr Leu Leu Thr His Pro Ser Asp Pro Leu Glu
 405 410 415

Leu Val Val Ser Gly Ala Ala Glu Thr Leu Ser Pro Pro Gln Asn Lys
 420 425 430

15 Ser Asp Ser Lys Ala Gly Glu
 435

(2) INFORMATION FOR SEQ ID NO:13:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2197 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
 30 (A) NAME/KEY: CDS
 (B) LOCATION: 191..1483

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

35 GTCGACCCAC GCGTCCGGTC AACTTTTCTT CCCCTACTTC CCTGCATTTC TCCTCTGTGC 60
 TCACTGCCAC ACGCAGCTCA ACCTGGACGG CACAGCCAGA TGCGAGATGC GTCTCTGCTG 120
 40 ATCTGAGTCT GCCTGCAGCA TGGACCTGGG TCTTCCCTGA AGCATCTCCA GGGCTGGAGG 180
 GACGACTGCC ATG CAC CGA GGG CTC ATC CAT CCG CAG AGC AGG GCA GTG 229
 Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val
 1 5 10
 45 GGA GGA GAC GCC ATG ACC CCC ATC GTC ACA GTC CTG ATC TGT CTC GGG 277
 Gly Gly Asp Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly
 15 20 25
 50 CTG AGT CTG GGC CCC AGG ACC CAC GTG CAG ACA GGG ACC ATC CCC AAG 325
 Leu Ser Leu Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys
 30 35 40 45
 55 CCC ACC CTG TGG GCT GAG CCA GAC TCT GTG ATC ACC CAG GGG AGT CCC 373
 Pro Thr Leu Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro
 50 55 60
 GTC ACC CTC AGT TGT CAG GGG AGC CTT GAA GCC CAG GAG TAC CGT CTA 421
 Val Thr Leu Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu
 65 70 75

5 TAT AGG GAG AAA AAA TCA GCA TCT TGG ATT ACA CGG ATA CGA CCA GAG 469
 Tyr Arg Glu Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu
 80 85 90

10 CTT GTG AAG AAC GGC CAG TTC CAC ATC CCA TCC ATC ACC TGG GAA CAC 517
 Leu Val Lys Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His
 95 100 105

15 ACA GGG CGA TAT GGC TGT CAG TAT TAC AGC CGC GCT CGG TGG TCT GAG 565
 Thr Gly Arg Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu
 110 115 120 125

20 CTC AGT GAC CCC CTG GTG CTG GTG ATG ACA GGA GCC TAC CCA AAA CCC 613
 Leu Ser Asp Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro
 130 135 140

25 ACC CTC TCA GCC CAG CCC AGC CCT GTG GTG ACC TCA GGA GGA AGG GTG 661
 Thr Leu Ser Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val
 145 150 155

30 ACC CTC CAG TGT GAG TCA CAG GTG GCA TTT GGC GGC TTC ATT CTG TGT 709
 Thr Leu Gln Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys
 160 165 170

35 AAG GAA GGA GAA GAT GAA CAC CCA CAA TGC CTG AAC TCC CAG CCC CAT 757
 Lys Glu Gly Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His
 175 180 185

40 GCC CGT GGG TCG TCC CGC GCC ATC TTC TCC GTG GGC CCC GTG AGC CCG 805
 Ala Arg Gly Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro
 190 195 200 205

45 AAT CGC AGG TGG TCG CAC AGG TGC TAT GGT TAT GAC TTG AAC TCT CCC 853
 Asn Arg Arg Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro
 210 215 220

50 TAT GTG TGG TCT TCA CCC AGT GAT CTC CTG GAG CTC CTG GTC CCA GGT 901
 Tyr Val Trp Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly
 225 230 235

55 GTT TCT AAG AAG CCA TCA CTC TCA GTG CAG CCG GGT CCT GTC GTG GCC 949
 Val Ser Lys Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala
 240 245 250

60 CCT GGG GAA AGC CTG ACC CTC CAG TGT GTC TCT GAT GTC GGC TAT GAC 997
 Pro Gly Glu Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp
 255 260 265

65 AGA TTT GTT CTG TAC AAG GAG GGG GAA CGT GAC CTT CGC CAG CTC CCT 1045
 Arg Phe Val Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro
 270 275 280 285

70 GGC CGG CAG CCC CAG GCT GGG CTC TCC CAG GCC AAC TTC ACC CTG GGC 1093
 Gly Arg Gln Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly
 290 295 300

75 CCT GTG AGC CGC TCC TAC GGG GGC CAG TAC AGA TGC TAC GGT GCA TAC 1141
 Pro Val Ser Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr

	305	310	315	
5	AAC CTC TCC TCC GAG TGG TCG GCC CCC AGC GAC CCC CTG GAC ATC CTG Asn Leu Ser Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu 320 325 330			1189
10	ATC ACA GGA CAG ATC CAT GGC ACA CCC TTC ATC TCA GTG CAG CCA GGC Ile Thr Gly Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly 335 340 345			1237
15	CCC ACA GTG GCC TCA GGA GAG AAC GTG ACC CTG CTG TGT CAG TCA TGG Pro Thr Val Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp 350 355 360 365			1285
20	CGG CAG TTC CAC ACT TTC CTT CTG ACC AAG GCG GGA GCA GAT GAT GCC Arg Gln Phe His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala 370 375 380			1333
25	CCA CTC CGT CTA AGA TCA ATA CAC GAA TAT CCT AAG TAC CAG GCT GAA Pro Leu Arg Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu 385 390 395			1381
30	TTC CCC ATG AGT CCT GTG ACC TCA GCC CAC GCG GGG ACC TAC AGG ACC Phe Pro Met Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Thr 400 405 410			1429
35	CTC CAT GGG TTC CAG CCC CCC ACC CAC CGG TCC CAT CTC CAC ACC TGC Leu His Gly Phe Gln Pro Pro Thr His Arg Ser His Leu His Thr Cys 415 420 425			1477
40	AGG CCC TGAGGACCAG CCCCTCACCC CCACTGGGTC GGATCCCCAA AGTGGTCTGG Arg Pro 430			1533
45	GAAGGCACCT GGGGGTTGTG ATCGGCATCT TGGTGGCCG CGTCCTACTG CTCCTCCTCC TCCTCCTCCT CTTCCTCATC CTCCGACATC GACGTCAGG CAAACACTGG ACATCGACCC AGAGAAAGGC TGATTTCCAA CATCCTGCAG GGGCTGTGG GCCAGAGCCC ACAGACAGAG GCCTGCAGTG GAGGTCCAGC CCAGCTGCCG ACGCCCAGGA AGAAAACCTC TATGCTGCCG TGAAGGACAC ACAGCCTGAA GATGGGGTGG AGATGACAC TCGGGCTGCT GCATCTGAAG CCCCCAGGA TGTGACCTAC GCCCAGCTGC ACAGCTTGAC CCTCAGACGG AAGGCAACTG AGCCTCCTCC ATCCCAGGAA AGGGAACCTC CACCTGAGCC CAGCATTAC GCCACCCTGG CCATCCACTA GCCCGGAGGG TACGCAGACT CCACACTCAG TAGAAGGAGA CTCAGGACTG CTGAAGGCAC GGGAGCTGCC CCCAGTGGAC ACCAATGAAC CCCAGTCAGC CTGGACCCCT AACAAAGACC ATGAGGAGAT GCTGGGAACT TTGGGACTCA CTTGATTCTG CAGTGGAAAT AACTAATATC CCTACATTTT TTAATTAAAT CAACAGACTT CTCAATAATC AATGAGTTAA CCGA			1593 1653 1713 1773 1833 1893 1953 2013 2073 2133 2193
55				2197

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 431 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp
 1 5 10 15

Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu
 20 25 30

Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu
 35 40 45

Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu
 50 55 60

Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu
 65 70 75 80

Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys
 85 90 95

Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg
 100 105 110

Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp
 115 120 125

Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser
 130 135 140

Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln
 145 150 155 160

Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly
 165 170 175

Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
 180 185 190

Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg
 195 200 205

Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp
 210 215 220

Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys
 225 230 235 240

Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
 245 250 255

Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val
 260 265 270
 5 Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln
 275 280 285
 Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 290 295 300
 10 Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser
 305 310 315 320
 Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly
 325 330 335
 15 Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val
 340 345 350
 Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe
 355 360 365
 20 His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg
 370 375 380
 25 Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met
 385 390 395 400
 Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Thr Leu His Gly
 405 410 415
 30 Phe Gln Pro Pro Thr His Arg Ser His Leu His Thr Cys Arg Pro
 420 425 430

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2271 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 191..2035

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCGACCCAC GCGTCCGGTC AACTTTTCTT CCCCTACTTC CCTGCATTTC TCCTCTGTGC 60
 TCACTGCCAC ACGCAGCTCA ACCTGGACGG CACAGCCAGA TGCGAGATGC GTCTCTGTCTG 120
 55 ATCTGAGTCT GCCTGCAGCA TGGACCTGGG TCTTCCCTGA AGCATCTCCA GGGCTGGAGG 180
 GACGACTGCC ATG CAC CGA GGG CTC ATC CAT CCG CAG AGC AGG GCA GTG 229
 Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val

	1	5	10			
5	GGA GGA GAC GCC ATG ACC CCC ATC GTC ACA GTC CTG ATC TGT CTC GGG Gly Gly Asp Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly	15	20	25	277	
10	CTG AGT CTG GGC CCC AGG ACC CAC GTG CAG ACA GGG ACC ATC CCC AAG Leu Ser Leu Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys	30	35	40	45	325
15	CCC ACC CTG TGG GCT GAG CCA GAC TCT GTG ATC ACC CAG GGG AGT CCC Pro Thr Leu Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro	50	55	60		373
20	GTC ACC CTC AGT TGT CAG GGG AGC CTT GAA GCC CAG GAG TAC CGT CTA Val Thr Leu Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu	65	70	75		421
25	TAT AGG GAG AAA AAA TCA GCA TCT TGG ATT ACA CGG ATA CGA CCA GAG Tyr Arg Glu Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu	80	85	90		469
30	CTT GTG AAG AAC GGC CAG TTC CAC ATC CCA TCC ATC ACC TGG GAA CAC Leu Val Lys Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His	95	100	105		517
35	ACA GGG CGA TAT GGC TGT CAG TAT TAC AGC CGC GCT CGG TGG TCT GAG Thr Gly Arg Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu	110	115	120	125	565
40	CTC AGT GAC CCC CTG GTG CTG GTG ATG ACA GGA GCC TAC CCA AAA CCC Leu Ser Asp Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro	130	135	140		613
45	ACC CTC TCA GCC CAG CCC AGC CCT GTG GTG ACC TCA GGA GGA AGG GTG Thr Leu Ser Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val	145	150	155		661
50	ACC CTC CAG TGT GAG TCA CAG GTG GCA TTT GGC GGC TTC ATT CTG TGT Thr Leu Gln Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys	160	165	170		709
55	AAG GAA GGA GAA GAT GAA CAC CCA CAA TGC CTG AAC TCC CAG CCC CAT Lys Glu Gly Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His	175	180	185		757
60	GCC CGT GGG TCG TCC CGC GCC ATC TTC TCC GTG GGC CCC GTG AGC CCG Ala Arg Gly Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro	190	195	200	205	805
65	AAT CGC AGG TGG TCG CAC AGG TGC TAT GGT TAT GAC TTG AAC TCT CCC Asn Arg Arg Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro	210	215	220		853
70	TAT GTG TGG TCT TCA CCC AGT GAT CTC CTG GAG CTC CTG GTC CCA GGT Tyr Val Trp Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly	225	230	235		901
75	GTT TCT AAG AAG CCA TCA CTC TCA GTG CAG CCG GGT CCT GTC GTG GCC					949

	Val	Ser	Lys	Lys	Pro	Ser	Leu	Ser	Val	Gln	Pro	Gly	Pro	Val	Val	Ala	
			240					245					250				
5	CCT	GGG	GAA	AGC	CTG	ACC	CTC	CAG	TGT	GTC	TCT	GAT	GTC	GGC	TAT	GAC	997
	Pro	Gly	Glu	Ser	Leu	Thr	Leu	Gln	Cys	Val	Ser	Asp	Val	Gly	Tyr	Asp	
		255					260					265					
10	AGA	TTT	GTT	CTG	TAC	AAG	GAG	GGG	GAA	CGT	GAC	CTT	CGC	CAG	CTC	CCT	1045
	Arg	Phe	Val	Leu	Tyr	Lys	Glu	Gly	Glu	Arg	Asp	Leu	Arg	Gln	Leu	Pro	
	270					275				280						285	
15	GGC	CGG	CAG	CCC	CAG	GCT	GGG	CTC	TCC	CAG	GCC	AAC	TTC	ACC	CTG	GGC	1093
	Gly	Arg	Gln	Pro	Gln	Ala	Gly	Leu	Ser	Gln	Ala	Asn	Phe	Thr	Leu	Gly	
					290					295					300		
20	CCT	GTG	AGC	CGC	TCC	TAC	GGG	GGC	CAG	TAC	AGA	TGC	TAC	GGT	GCA	TAC	1141
	Pro	Val	Ser	Arg	Ser	Tyr	Gly	Gly	Gln	Tyr	Arg	Cys	Tyr	Gly	Ala	Tyr	
				305					310					315			
25	AAC	CTC	TCC	TCC	GAG	TGG	TCG	GCC	CCC	AGC	GAC	CCC	CTG	GAC	ATC	CTG	1189
	Asn	Leu	Ser	Ser	Glu	Trp	Ser	Ala	Pro	Ser	Asp	Pro	Leu	Asp	Ile	Leu	
			320					325					330				
30	ATC	ACA	GGA	CAG	ATC	CAT	GGC	ACA	CCC	TTC	ATC	TCA	GTG	CAG	CCA	GGC	1237
	Ile	Thr	Gly	Gln	Ile	His	Gly	Thr	Pro	Phe	Ile	Ser	Val	Gln	Pro	Gly	
		335					340					345					
35	CCC	ACA	GTG	GCC	TCA	GGA	GAG	AAC	GTG	ACC	CTG	CTG	TGT	CAG	TCA	TGG	1285
	Pro	Thr	Val	Ala	Ser	Gly	Glu	Asn	Val	Thr	Leu	Leu	Cys	Gln	Ser	Trp	
	350					355					360					365	
40	CGG	CAG	TTC	CAC	ACT	TTC	CTT	CTG	ACC	AAG	GCG	GGA	GCA	GCT	GAT	GCC	1333
	Arg	Gln	Phe	His	Thr	Phe	Leu	Leu	Thr	Lys	Ala	Gly	Ala	Ala	Asp	Ala	
					370					375					380		
45	CCA	CTC	CGT	CTA	AGA	TCA	ATA	CAC	GAA	TAT	CCT	AAG	TAC	CAG	GCT	GAA	1381
	Pro	Leu	Arg	Leu	Arg	Ser	Ile	His	Glu	Tyr	Pro	Lys	Tyr	Gln	Ala	Glu	
				385					390					395			
50	TTC	CCC	ATG	AGT	CCT	GTG	ACC	TCA	GCC	CAC	GCG	GGG	ACC	TAC	AGG	TGC	1429
	Phe	Pro	Met	Ser	Pro	Val	Thr	Ser	Ala	His	Ala	Gly	Thr	Tyr	Arg	Cys	
			400					405					410				
55	TAC	GGC	TCA	CTC	AAC	TCC	GAC	CCC	TAC	CTG	CTG	TCT	CAC	CCC	AGT	GAG	1477
	Tyr	Gly	Ser	Leu	Asn	Ser	Asp	Pro	Tyr	Leu	Leu	Ser	His	Pro	Ser	Glu	
		415					420					425					
60	CCC	CTG	GAG	CTC	GTG	GTC	TCA	GGA	CCC	TCC	ATG	GGT	TCC	AGC	CCC	CCA	1525
	Pro	Leu	Glu	Leu	Val	Val	Ser	Gly	Pro	Ser	Met	Gly	Ser	Ser	Pro	Pro	
	430					435					440					445	
65	CCC	ACC	GGT	CCC	ATC	TCC	ACA	CCT	GCA	GGC	CCT	GAG	GAC	CAG	CCC	CTC	1573
	Pro	Thr	Gly	Pro	Ile	Ser	Thr	Pro	Ala	Gly	Pro	Glu	Asp	Gln	Pro	Leu	
					450					455					460		
70	ACC	CCC	ACT	GGG	TCG	GAT	CCC	CAA	AGT	GGT	CTG	GGA	AGG	CAC	CTG	GGG	1621
	Thr	Pro	Thr	Gly	Ser	Asp	Pro	Gln	Ser	Gly	Leu	Gly	Arg	His	Leu	Gly	
				465					470					475			

GTT GTG ATC GGC ATC TTC GTG GCC GTC GTC CTA CTG CTC CTC CTC CTC 1669
 Val Val Ile Gly Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu
 480 485 490

5 CTC CTC CTC TTC CTC ATC CTC CGA CAT CGA CGT CAG GGC AAA CAC TGG 1717
 Leu Leu Leu Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp
 495 500 505

10 ACA TCG ACC CAG AGA AAG GCT GAT TTC CAA CAT CCT GCA GGG GCT GTG 1765
 Thr Ser Thr Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val
 510 515 520 525

15 GGG CCA GAG CCC ACA GAC AGA GGC CTG CAG TGG AGG TCC AGC CCA GCT 1813
 Gly Pro Glu Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala
 530 535 540

20 GCC GAC GCC CAG GAA GAA AAC CTC TAT GCT GCC GTG AAG GAC ACA CAG 1861
 Ala Asp Ala Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys Asp Thr Gln
 545 550 555

25 CCT GAA GAT GGG GTG GAG ATG GAC ACT CGG GCT GCT GCA TCT GAA GCC 1909
 Pro Glu Asp Gly Val Glu Met Asp Thr Arg Ala Ala Ala Ser Glu Ala
 560 565 570

30 CCC CAG GAG GTG ACC TAC GCC CAG CTG CAC AGC TTG ACC CTC AGA CGG 1957
 Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg
 575 580 585

35 AAG GCA ACT GAG CCT CCT CCA TCC CAG GAA AGG GAA CCT CCA GCT GAG 2005
 Lys Ala Thr Glu Pro Pro Pro Ser Gln Glu Arg Glu Pro Pro Ala Glu
 590 595 600 605

40 CCC AGC ATT TAC GCC ACC CTG GCC ATC CAC TAGCCCGGAG GGTACGCAGA 2055
 Pro Ser Ile Tyr Ala Thr Leu Ala Ile His
 610 615

45 CTCACACTC AGTAGAAGGA GACTCAGGAC TGCTGAAGGC ACGGGAGCTG CCCCCAGTGG 2115
 ACACCAATGA ACCCCAGTCA GCCTGGACCC CTAACAAAGA CCATGAGGAG ATGCTGGGAA 2175
 CTTTGGGACT CACTTGATTC TGCAGTGGAA ATAACATAA TCCCTACATT TTTTAATTAA 2235
 AGCAACAGAC TTCTCAATAA TCAATGAGTT AACCGA 2271

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 615 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp
 1 5 10 15

Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu
 20 25 30
 5 Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu
 35 40 45
 Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu
 50 55 60
 10 Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu
 65 70 75 80
 Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys
 85 90 95
 15 Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg
 100 105 110
 Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp
 115 120 125
 20 Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser
 130 135 140
 25 Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln
 145 150 155 160
 Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly
 165 170 175
 30 Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
 180 185 190
 Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg
 195 200 205
 Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp
 210 215 220
 40 Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys
 225 230 235 240
 Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
 245 250 255
 45 Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val
 260 265 270
 Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln
 275 280 285
 50 Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 290 295 300
 Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser
 305 310 315 320
 Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly
 325 330 335

Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val
 340 345 350
 5 Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe
 355 360 365
 His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg
 370 375 380
 10 Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met
 385 390 395 400
 Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser
 405 410 415
 15 Leu Asn Ser Asp Pro Tyr Leu Leu Ser His Pro Ser Glu Pro Leu Glu
 420 425 430
 20 Leu Val Val Ser Gly Pro Ser Met Gly Ser Ser Pro Pro Pro Thr Gly
 435 440 445
 Pro Ile Ser Thr Pro Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr
 450 455 460
 25 Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile
 465 470 475 480
 Gly Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu Leu Leu
 485 490 495
 30 Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr
 500 505 510
 35 Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu
 515 520 525
 Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala
 530 535 540
 40 Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys Asp Thr Gln Pro Glu Asp
 545 550 555 560
 Gly Val Glu Met Asp Thr Arg Ala Ala Ala Ser Glu Ala Pro Gln Asp
 565 570 575
 45 Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys Ala Thr
 580 585 590
 50 Glu Pro Pro Pro Ser Gln Glu Arg Glu Pro Pro Ala Glu Pro Ser Ile
 595 600 605
 Tyr Ala Thr Leu Ala Ile His
 610 615
 55

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2388 base pairs

87

(B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

10 (A) NAME/KEY: CDS
 (B) LOCATION: 180..2024

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

15	AAAGAAGTCA ACTTTTCTTC CCCTACTTCC CTGCATTTCT CCTCTGTGCT CACTGCCACA	60
	CGCAGCTCAA CCTGGACGGC ACAGCCAGAT GCGAGATGCG TCTCTGCTGA TCTGAGTCTG	120
	CCTGCAGCAT GGACCTGGGT CTTCCCTGAA GCATCTCCAG GGCTGGAGGG ACGACTGCC	179
20	ATG CAC CGA GGG CTC ATC CAT CCG CAG AGC AGG GCA GTG GGA GGA GAC	227
	Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp	
	1 5 10 15	
25	GCC ATG ACC CCC ATC GTC ACA GTC CTG ATC TGT CTC GGG CTG AGT CTG	275
	Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu	
	20 25 30	
30	GGC CCC AGG ACC CAC GTG CAG ACA GGG ACC ATC CCC AAG CCC ACC CTG	323
	Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu	
	35 40 45	
	TGG GCT GAG CCA GAC TCT GTG ATC ACC CAG GGG AGT CCC GTC ACC CTC	371
35	Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu	
	50 55 60	
	AGT TGT CAG GGG AGC CTT GAA GCC CAG GAG TAC CGT CTA TAT AGG GAG	419
	Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu	
	65 70 75 80	
40	AAA AAA TCA GCA TCT TGG ATT ACA CGG ATA CGA CCA GAG CTT GTG AAG	467
	Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys	
	85 90 95	
45	AAC GGC CAG TTC CAC ATC CCA TCC ATC ACC TGG GAA CAC ACA GGG CGA	515
	Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg	
	100 105 110	
50	TAT GGC TGT CAG TAT TAC AGC CGC GCT CGG TGG TCT GAG CTC AGT GAC	563
	Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp	
	115 120 125	
	CCC CTG GTG CTG GTG ATG ACA GGA GCC TAC CCA AAA CCC ACC CTC TCA	611
55	Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser	
	130 135 140	
	GCC CAG CCC AGC CCT GTG GTG ACC TCA GGA GGA AGG GTG ACC CTC CAG	659
	Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln	
	145 150 155 160	

	TGT GAG TCA CAG GTG GCA TTT GGC GGC TTC ATT CTG TGT AAG GAA GGA	707
	Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly	
	165 170 175	
5	GAA GAT GAA CAC CCA CAA TGC CTG AAC TCC CAG CCC CAT GCC CGT GGG	755
	Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly	
	180 185 190	
10	TCG TCC CGC GCC ATC TTC TCC GTG GGC CCC GTG AGC CCG AAT CGC AGG	803
	Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg	
	195 200 205	
15	TGG TCG CAC AGG TGC TAT GGT TAT GAC TTG AAC TCT CCC TAT GTG TGG	851
	Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp	
	210 215 220	
20	TCT TCA CCC AGT GAT CTC CTG GAG CTC CTG GTC CCA GGT GTT TCT AAG	899
	Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys	
	225 230 235 240	
25	AAG CCA TCA CTC TCA GTG CAG CCG GGT CCT GTC GTG GCC CCT GGG GAA	947
	Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu	
	245 250 255	
30	AGC CTG ACC CTC CAG TGT GTC TCT GAT GTC GGC TAT GAC AGA TTT GTT	995
	Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val	
	260 265 270	
35	CTG TAC AAG GAG GGG GAA CGT GAC CTT CGC CAG CTC CCT GGC CGG CAG	1043
	Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln	
	275 280 285	
40	CCC CAG GCT GGG CTC TCC CAG GCC AAC TTC ACC CTG GGC CCT GTG AGC	1091
	Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser	
	290 295 300	
45	CGC TCC TAC GGG GGC CAG TAC AGA TGC TAC GGT GCA TAC AAC CTC TCC	1139
	Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser	
	305 310 315 320	
50	TCC GAG TGG TCG GCC CCC AGC GAC CCC CTG GAC ATC CTG ATC ACA GGA	1187
	Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly	
	325 330 335	
55	CAG ATC CAT GGC ACA CCC TTC ATC TCA GTG CAG CCA GGC CCC ACA GTG	1235
	Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val	
	340 345 350	
60	GCC TCA GGA GAG AAC GTG ACC CTG CTG TGT CAG TCA TGG CGG CAG TTC	1283
	Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe	
	355 360 365	
65	CAC ACT TTC CTT CTG ACC AAG GCG GGA GCA GCT GAT GCC CCA CTC CGT	1331
	His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg	
	370 375 380	
70	CTA AGA TCA ATA CAC GAA TAT CCT AAG TAC CAG GCT GAA TTC CCC ATG	1379
	Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met	

	385		390		395		400	
5	AGT CCC GTG ACC TCA GCC CAC GCG GGG ACC TAC AGG TGC TAC GGC TCA Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser	1427						
	405		410		415			
10	CTC AAC TCC GAC CCC TAC CTG CTG TCT CAC CCC AGT GAG CCC CTG GAG Leu Asn Ser Asp Pro Tyr Leu Leu Ser His Pro Ser Glu Pro Leu Glu	1475						
	420		425		430			
	CTC GTG GTC TCA GGA CCC TCC ATG GGT TCC AGC CCC CCA CCC ACC GGT Leu Val Val Ser Gly Pro Ser Met Gly Ser Ser Pro Pro Pro Thr Gly	1523						
	435		440		445			
15	CCC ATC TCC ACA CCT GCA GGC CCT GAG GAC CAG CCC CTC ACC CCC ACT Pro Ile Ser Thr Pro Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr	1571						
	450		455		460			
20	GGG TCG GAT CCC CAA AGT GGT CTG GGA AGG CAC CTG GGG GTT GTG ATC Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile	1619						
	465		470		475		480	
25	GGC ATC TTG GTG GCC GTC GTC CTA CTG CTC CTC CTC CTC CTC CTC CTC Gly Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu Leu Leu	1667						
	485		490		495			
30	TTC CTC ATC CTC CGA CAT CGA CGT CAG GGC AAA CAC TGG ACA TCG ACC Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr	1715						
	500		505		510			
	CAG AGA AAG GCT GAT TTC CAA CAT CCT GCA GGG GCT GTG GGG CCA GAG Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu	1763						
	515		520		525			
35	CCC ACA GAC AGA GGC CTG CAG TGG AGG TCC AGC CCA GCT GCC GAC GCC Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala	1811						
	530		535		540			
40	CAG GAA GAA AAC CTC TAT GCT GCC GTG AAG GAC ACA CAG CCT GAA GAT Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys Asp Thr Gln Pro Glu Asp	1859						
	545		550		555		560	
45	GGG GTG GAG ATG GAC ACT CGG GCT GCT GCA TCT GAA GCC CCC CAG GAT Gly Val Glu Met Asp Thr Arg Ala Ala Ala Ser Glu Ala Pro Gln Asp	1907						
	565		570		575			
50	GTG ACC TAC GCC CAG CTG CAC AGC TTG ACC CTC AGA CGG AAG GCA ACT Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys Ala Thr	1955						
	580		585		590			
	GAG CCT CCT CCA TCC CAG GAA AGG GAA CCT CCA GCT GAG CCC AGC ATC Glu Pro Pro Pro Ser Gln Glu Arg Glu Pro Pro Ala Glu Pro Ser Ile	2003						
	595		600		605			
55	TAC GCC ACC CTG GCC ATC CAC TAGCCCGGAG GGTACGCAGA CTCCACACTC Tyr Ala Thr Leu Ala Ile His	2054						
	610		615					
	AGTAGAAGGA GACTCAGGAC TGCTGAAGGC ACGGGAGCTG CCCCCAGTGG ACACCAATGA	2114						

87

5
 10
 ACCCCAGTCA GCCTGGACCC CTAACAAAGA CCATGAGGAG ATGCTGGGAA CTTTGGGACT 2174
 CACTTGATTC TGCAGTCGAA ATAAC TAATA TCCCTACATT TTTTAATTAA AGCAACAGAC 2234
 TTCTCAATAA TCAATGAGTT AACCGAGAAA ACTAAAATCA GAAGTAAGAA TGTGCTTTAA 2294
 ACTGAATCAC AATATAAATA TTACACATCA CACAATGAAA TTGAAAAAGT ACAAACCACA 2354
 AATGAAAAAA GTAGAAACGA AAAAAAAAAA AAAA 2388

(2) INFORMATION FOR SEQ ID NO:18:

15 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 615 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

25 Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp
 1 5 10 15
 Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu
 20 25 30
 30 Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu
 35 40 45
 Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu
 50 55 60
 35 Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu
 65 70 75 80
 40 Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys
 85 90 95
 Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg
 100 105 110
 45 Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp
 115 120 125
 Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser
 130 135 140
 50 Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln
 145 150 155 160
 55 Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly
 165 170 175
 Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
 180 185 190

Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg
 195 200 205
 5 Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp
 210 215 220
 Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys
 225 230 235 240
 10 Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
 245 250 255
 Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val
 260 265 270
 15 Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln
 275 280 285
 Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 290 295 300
 20 Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser
 305 310 315 320
 25 Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly
 325 330 335
 Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val
 340 345 350
 30 Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe
 355 360 365
 His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg
 370 375 380
 35 Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met
 385 390 395 400
 40 Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser
 405 410 415
 Leu Asn Ser Asp Pro Tyr Leu Leu Ser His Pro Ser Glu Pro Leu Glu
 420 425 430
 45 Leu Val Val Ser Gly Pro Ser Met Gly Ser Ser Pro Pro Pro Thr Gly
 435 440 445
 Pro Ile Ser Thr Pro Ala Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr
 450 455 460
 Gly Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile
 465 470 475 480
 55 Gly Ile Leu Val Ala Val Val Leu Leu Leu Leu Leu Leu Leu Leu
 485 490 495
 Phe Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr
 500 505 510

Gln Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu
 515 520 525
 5 Pro Thr Asp Arg Gly Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala
 530 535 540
 Gln Glu Glu Asn Leu Tyr Ala Ala Val Lys Asp Thr Gln Pro Glu Asp
 545 550 555 560
 10 Gly Val Glu Met Asp Thr Arg Ala Ala Ala Ser Glu Ala Pro Gln Asp
 565 570 575
 Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys Ala Thr
 580 585 590
 15 Glu Pro Pro Pro Ser Gln Glu Arg Glu Pro Pro Ala Glu Pro Ser Ile
 595 600 605
 20 Tyr Ala Thr Leu Ala Ile His
 610 615

(2) INFORMATION FOR SEQ ID NO:19:

25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2200 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: cDNA

35 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 174..1466

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

40 GTCAACTTTT CTTCCCCTAC TTCCCTGCAT TTCTCCTCTG TGCTCACTGC CACACGCAGC 60
 TCAACCTGGA CGGCACAGCC AGATGCGAGA TCGTCTCTG CTGATCTGAG TCTGCCTGCA 120
 45 GCATGGACCT GGGTCTTCCC TGAAGCATCT CCAGGGCTGG AGGGACGACT GCC ATG 176
 Met
 1
 CAC CGA GGG CTC ATC CAT CCG CAG AGC AGG GCA GTG GGA GGA GAC GCC 224
 50 His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp Ala
 5 10 15
 ATG ACC CCC ATC GTC ACA GTC CTG ATC TGT CTC GGG CTG AGT CTG GGC 272
 55 Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
 20 25 30
 CCC AGG ACC CAC GTG CAG ACA GGG ACC ATC CCC AAG CCC ACC CTG TGG 320
 Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu Trp
 35 40 45

5	GCT GAG CCA GAC TCT GTG ATC ACC CAG GGG AGT CCC GTC ACC CTC AGT Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Ser 50 55 60 65	368
10	TGT CAG GGG AGC CTT GAA GCC CAG GAG TAC CGT CTA TAT AGG GAG AAA Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu Lys 70 75 80	416
15	AAA TCA GCA TCT TGG ATT ACA CGG ATA CGA CCA GAG CTT GTG AAG AAC Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys Asn 85 90 95	464
20	GGC CAG TTC CAC ATC CCA TCC ATC ACC TGG GAA CAC ACA GGG CGA TAT Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg Tyr 100 105 110	512
25	GGC TGT CAG TAT TAC AGC CGC GCT CGG TGG TCT GAG CTC AGT GAC CCC Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp Pro 115 120 125	560
30	CTG GTG CTG GTG ATG ACA GGA GCC TAC CCA AAA CCC ACC CTC TCA GCC Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser Ala 130 135 140 145	608
35	CAG CCC AGC CCT GTG GTG ACC TCA GGA GGA AGG GTG ACC CTC CAG TGT Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln Cys 150 155 160	656
40	GAG TCA CAG GTG GCA TTT GGC GGC TTC ATT CTG TGT AAG GAA GGA GAA Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly Glu 165 170 175	704
45	GAT GAA CAC CCA CAA TGC CTG AAC TCC CAG CCC CAT GCC CGT GGG TCG Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly Ser 180 185 190	752
50	TCC CGC GCC ATC TTC TCC GTG GGC CCC GTG AGC CCG AAT CGC AGG TGG Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg Trp 195 200 205	800
55	TCG CAC AGG TGC TAT GGT TAT GAC TTG AAC TCT CCC TAT GTG TGG TCT Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp Ser 210 215 220 225	848
60	TCA CCC AGT GAT CTC CTG GAG CTC CTG GTC CCA GGT GTT TCT AAG AAG Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys Lys 230 235 240	896
65	CCA TCA CTC TCA GTG CAG CCG GGT CCT GTC GTG GCC CCT GGG GAA AGC Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu Ser 245 250 255	944
70	CTG ACC CTC CAG TGT GTC TCT GAT GTC GGC TAT GAC AGA TTT GTT CTG Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val Leu 260 265 270	992
75	TAC AAG GAG GGG GAA CGT GAC CTT CGC CAG CTC CCT GGC CGG CAG CCC Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln Pro 280 285 290 295	1040

	275	280	285	
5	CAG GCT GGG CTC TCC CAG GCC AAC TTC ACC CTG GGC CCT GTG AGC CGC Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser Arg 290 295 300 305	1088		
10	TCC TAC GGG GGC CAG TAC AGA TGC TAC GGT GCA TAC AAC CTC TCC TCC Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser Ser 310 315 320	1136		
15	GAG TGG TCG GCC CCC AGC GAC CCC CTG GAC ATC CTG ATC ACA GGA CAG Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly Gln 325 330 335	1184		
20	ATC CAT GGC ACA CCC TTC ATC TCA GTG CAG CCA GGC CCC ACA GTG GCC Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Thr Val Ala 340 345 350	1232		
25	TCA GGA GAG AAC GTG ACC CTG CTG TGT CAG TCA TGG CGG CAG TTC CAC Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe His 355 360 365	1280		
30	ACT TTC CTT CTG ACC AAG GCG GGA GCA GCT GAT GCC CCA CTC CGT CTA Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg Leu 370 375 380 385	1328		
35	AGA TCA ATA CAC GAA TAT CCT AAG TAC CAG GCT GAA TTC CCC ATG AGT Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met Ser 390 395 400	1376		
40	CCT GTG ACC TCA GCC CAC GCG GGG ACC TAC AGG ACC CTC CAT GGG TTC Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Thr Leu His Gly Phe 405 410 415	1424		
45	CAG CCC CCC ACC CAC CGG TCC CAT CTC CAC ACC TGC AGG CCC Gln Pro Pro Thr His Arg Ser His Leu His Thr Cys Arg Pro 420 425 430	1466		
50	TGAGGACCAG CCCCTCACCC CCACTGGGTC GGATCCCCAA AGTGGTCTGG GAAGGCACCT GGGGGTTGTG ATCGGCATCT TGGTGGCCGT CGTCCTACTG CTCCTCCTCC TCCTCCTCCT CTTCCTCATC CTCCGACATC GACGTCAGGG CAAACACTGG ACATCGACCC AGAGAAAGGC TGATTTCCAA CATCCTGCAG GGGCTGTGGG GCCAGAGCCC ACAGACAGAG GCCTGCAGTG GAGGTCCAGC CCAGCTGCCG ACGCCCAGGA AGAAAACCTC TATGCTGCCG TGAAGGACAC ACAGCCTGAA GATGGGGTGG AGATGGACAC TCGGGTGCT GCATCTGAAG CCCCCAGGA TGTGACCTAC GCCCAGCTGC ACAGCTTGAC CCTCAGACGG AAGGCAACTG AGCCTCCTCC ATCCCAGGAA AGGGAACCTC CAGCTGAGCC CAGCATCTAC GCCACCCTGG CCATCCACTA GCCCCGAGGG TACGCAGACT CCACACTCAG TAGAAGGAGA CTCAGGACTG CTGAAGGCAC GGGAGCTGCC CCCAGTGAC ACCAATGAAC CCCAGTCAGC CTGGACCCCT AACAAAGACC ATGAGGAGAT GCTGGGAACT TTGGGACTCA CTTGATTCTG CAGTCGAAAT AACTAATATC	1526 1586 1646 1706 1766 1826 1886 1946 2006 2066 2126		

CCTACATTTT TTAATTAAAG CAACAGACTT CTCAATAATC AATGAGTTAA CCGAGAAAAC 2186
 TAAAAAAAAA AAAA 2200

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 431 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met His Arg Gly Leu Ile His Pro Gln Ser Arg Ala Val Gly Gly Asp
 1 5 10 15
 Ala Met Thr Pro Ile Val Thr Val Leu Ile Cys Leu Gly Leu Ser Leu
 20 25 30
 Gly Pro Arg Thr His Val Gln Thr Gly Thr Ile Pro Lys Pro Thr Leu
 25 35 40 45
 Trp Ala Glu Pro Asp Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu
 50 55 60
 Ser Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Arg Leu Tyr Arg Glu
 30 65 70 75 80
 Lys Lys Ser Ala Ser Trp Ile Thr Arg Ile Arg Pro Glu Leu Val Lys
 35 85 90 95
 Asn Gly Gln Phe His Ile Pro Ser Ile Thr Trp Glu His Thr Gly Arg
 100 105 110
 Tyr Gly Cys Gln Tyr Tyr Ser Arg Ala Arg Trp Ser Glu Leu Ser Asp
 40 115 120 125
 Pro Leu Val Leu Val Met Thr Gly Ala Tyr Pro Lys Pro Thr Leu Ser
 130 135 140
 Ala Gln Pro Ser Pro Val Val Thr Ser Gly Gly Arg Val Thr Leu Gln
 45 145 150 155 160
 Cys Glu Ser Gln Val Ala Phe Gly Gly Phe Ile Leu Cys Lys Glu Gly
 50 165 170 175
 Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly
 180 185 190
 Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Asn Arg Arg
 55 195 200 205
 Trp Ser His Arg Cys Tyr Gly Tyr Asp Leu Asn Ser Pro Tyr Val Trp
 210 215 220

Ser Ser Pro Ser Asp Leu Leu Glu Leu Leu Val Pro Gly Val Ser Lys
 225 230 235 240
 Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Val Val Ala Pro Gly Glu
 245 250 255
 Ser Leu Thr Leu Gln Cys Val Ser Asp Val Gly Tyr Asp Arg Phe Val
 260 265 270
 Leu Tyr Lys Glu Gly Glu Arg Asp Leu Arg Gln Leu Pro Gly Arg Gln
 275 280 285
 Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser
 290 295 300
 Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala Tyr Asn Leu Ser
 305 310 315 320
 Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Thr Gly
 325 330 335
 Gln Ile His Gly Thr Pro Phe Ile Ser Val Gln Pro Gly Pro Thr Val
 340 345 350
 Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp Arg Gln Phe
 355 360 365
 His Thr Phe Leu Leu Thr Lys Ala Gly Ala Ala Asp Ala Pro Leu Arg
 370 375 380
 Leu Arg Ser Ile His Glu Tyr Pro Lys Tyr Gln Ala Glu Phe Pro Met
 385 390 395 400
 Ser Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Thr Leu His Gly
 405 410 415
 Phe Gln Pro Pro Thr His Arg Ser His Leu His Thr Cys Arg Pro
 420 425 430
 (2) INFORMATION FOR SEQ ID NO:21:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2790 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: cDNA
 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 177..2132
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1722
 (D) OTHER INFORMATION: /note= N at nucleotide 1722 may be A, C,
 G, or T"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

5	GCCACACGCA GCTCAGCCTG GGCGGCACAG CCAGATGCGA GATGCGTCTC TGCTGATCTG	60
	AGTCTGCCTG CAGCATGGAC CTGGGTCTTC CCTGAAGCAT CTCCAGGGCT GGAGGGACGA	120
10	CTGCCATGCA CCGAGGGCTC ATCCATCCAC AGAGCAGGGC AGTGGGAGGA GACGCC	176
	ATG ACC CCC ATC CTC ACG GTC CTG ATC TGT CTC GGG CTG AGT CTG GGC	224
	Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly	
	1 5 10 15	
15	CCC CGG ACC CAC GTG CAG GCA GGG CAC CTC CCC AAG CCC ACC CTC TGG	272
	Pro Arg Thr His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp	
	20 25 30	
20	GCT GAA CCA GGC TCT GTG ATC ACC CAG GGG AGT CCT GTG ACC CTC AGG	320
	Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Arg	
	35 40 45	
	TGT CAG GGG GGC CAG GAG ACC CAG GAG TAC CGT CTA TAT AGA GAA AAG	368
25	Cys Gln Gly Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys	
	50 55 60	
	AAA ACA GCA CCC TGG ATT ACA CGG ATC CCA CAG GAG CTT GTG AAG AAG	416
	Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys	
	65 70 75 80	
30	GGC CAG TTC CCC ATC CCA TCC ATC ACC TGG GAA CAT GCA GGG CGG TAT	464
	Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr	
	85 90 95	
35	CGC TGT TAC TAT GGT AGC GAC ACT GCA GGC CGC TCA GAG AGC AGT GAC	512
	Arg Cys Tyr Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser Ser Asp	
	100 105 110	
40	CCC CTG GAG CTG GTG GTG ACA GGA GCC TAC ATC AAA CCC ACC CTC TCA	560
	Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser	
	115 120 125	
	GCC CAG CCC AGC CCC GTG GTG AAC TCA GGA GGG AAT GTA ACC CTC CAG	608
45	Ala Gln Pro Ser Pro Val Val Asn Ser Gly Gly Asn Val Thr Leu Gln	
	130 135 140	
	TGT GAC TCA CAG GTG GCA TTT GAT GGC TTC ATT CTG TGT AAG GAA GGA	656
50	Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ile Leu Cys Lys Glu Gly	
	145 150 155 160	
	GAA GAT GAA CAC CCA CAA TGC CTG AAC TCC CAG CCC CAT GCC CGT GGG	704
	Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly	
	165 170 175	
55	TCG TCC CGC GCC ATC TTC TCC GTG GGC CCC GTG AGC CCG AGT CGC AGG	752
	Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg	
	180 185 190	
	TGG TGG TAC AGG TGC TAT GCT TAT GAC TCG AAC TCT CCC TAT GAG TGG	800

	Trp Trp Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr Glu Trp	
	195 200 205	
5	TCT CTA CCC ACT GAT CTC CTG GAG CTC CTG GTC CTA GGT GTT TCT AAG Ser Leu Pro er Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser Lys	848
	210 215 220	
10	AAG CCA TCA CTC TCA GTG CAG CCA GGT CCT ATC GTG GCC CCT GAG GAG Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Glu Glu	896
	225 230 235 240	
15	ACC CTG ACT CTG CAG TGT GGC TCT GAT GCT GGC TAC AAC AGA TTT GTT Thr Leu Thr Leu Gln Cys Gly Ser Asp Ala Gly Tyr Asn Arg Phe Val	944
	245 250 255	
20	CTG TAC AAG GAC GGG GAA CGT GAC TTC CTT CAG CTC GCT GGC GCA CAG Leu Tyr Lys Asp Gly Glu Arg Asp Phe Leu Gln Leu Ala Gly Ala Gln	992
	260 265 270	
25	CCC CAG GCT GGG CTC TCC CAG GCC AAC TTC ACC CTG GGC CCT GTG AGC Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser	1040
	275 280 285	
30	CCC TCC TAC GGG GGC CAG TAC AGA TGC TAC GGT GCA CAC AAC CTC TCC Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser	1088
	290 295 300	
35	TCC GAG TGG TCG GCC CCC AGC GAC CCC CTG GAC ATC CTG ATC GCA GGA Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly	1136
	305 310 315 320	
40	CAG TTC TAT GAC AGA GTC TCC CTC TCG GTG CAG CCG GGC CCC ACG GTG Gln Phe Tyr Asp Arg Val Ser Leu Ser Val Gln Pro Gly Pro Thr Val	1184
	325 330 335	
45	GCC TCA GGA GAG AAC GTG ACC CTG CTG TGT CAG TCA CAG GGA TGG ATG Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Gln Gly Trp Met	1232
	340 345 350	
50	CAA ACT TTC CTT CTG ACC AAG GAG GGG GCA GCT GAT GAC CCA TGG CGT Gln Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala Asp Asp Pro Trp Arg	1280
	355 360 365	
55	CTA AGA TCA ACG TAC CAA TCT CAA AAA TAC CAG GCT GAA TTC CCC ATG Leu Arg Ser Thr Tyr Gln Ser Gln Lys Tyr Gln Ala Glu Phe Pro Met	1328
	370 375 380	
60	GGT CCT GTG ACC TCA GCC CAT GCG GGG ACC TAC AGG TGC TAC GGC TCA Gly Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser	1376
	385 390 395 400	
65	CAG AGC TCC AAA CCC TAC CTG CTG ACT CAC CCC AGT GAC CCC CTG GAG Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp Pro Leu Glu	1424
	405 410 415	
70	CTC GTG GTC TCA GGA CCG TCT GGG GGC CCC AGC TCC CCG ACA ACA GGC Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly	1472
	420 425 430	

	CCC ACC TCC ACA TCT GGC CCT GAG GAC CAG CCC CTC ACC CCC ACC GGG	1520
	Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly	
	435 440 445	
5	TCG GAT CCC CAG AGT GGT CTG GGA AGG CAC CTG GGG GTT GTG ATC GGC	1568
	Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly	
	450 455 460	
10	ATC TTG GTG GCC GTC ATC CTA CTG CTC CTC CTC CTC CTC CTC TTC	1616
	Ile Leu Val Ala Val Ile Leu Leu Leu Leu Leu Leu Leu Leu Phe	
	465 470 475 480	
15	CTC ATC CTC CGA CAT CGA CGT CAG GGC AAA CAC TGG ACA TCG ACC CAG	1664
	Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln	
	485 490 495	
20	AGA AAG GCT GAT TTC CAA CAT CCT GCA GGG GCT GTG GGG CCA GAG CCC	1712
	Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro	
	500 505 510	
25	ACA GAC AGA NGC CTG CAG TGG AGG TCC AGC CCA GCT GCC GAT GCC CAG	1760
	Thr Asp Arg Arg Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln	
	515 520 525	
30	GAA GAA AAC CTC TAT GCT GCC GTG AAG CAC ACA CAG CCT GAG GAT GGG	1808
	Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly	
	530 535 540	
35	GTG GAG ATG GAC ACT CGG CAG AGC CCA CAC GAT GAA GAC CCC CAG GCA	1856
	Val Glu Met Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln Ala	
	545 550 555 560	
40	GTG ACG TAT GCC GAG GTG AAA CAC TCC AGA CCT AGG AGA GAA ATG GCT	1904
	Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala	
	565 570 575	
45	TCT CCT CCT TCC CCA CTG TCT GGG GAA TTC CTG GAC ACA AAG GAC AGA	1952
	Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg	
	580 585 590	
50	CAG GCG GAA GAG GAC AGG CAG ATG GAC ACT GAG GCT GCT GCA TCT GAA	2000
	Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ser Glu	
	595 600 605	
55	GCC CCC CAG GAT GTG ACC TAC GCC CAG CTG CAC AGC TTG ACC CTT AGA	2048
	Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg	
	610 615 620	
60	CGG AAG GCA ACT GAG CCT CCT CCA TCC CAG GAA GGG CCC TCT CCA GCT	2096
	Arg Lys Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala	
	625 630 635 640	
65	GTG CCC AGC ATC TAC GCC ACT CTG GCC ATC CAC TAG CCCAGGGGGG	2142
	Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His *	
	645 650	
	GACGCAGACC CCACACTCCA TGGAGTCTGG AATGCATGGG AGCTGCCCCC CCAGTGGACA	2202
	CCATTGGACC CCACCCAGCC TGGATCTACC CCAGGAGACT CTGGGAACTT TTAGGGGTCA	2262

CTCAATTCTG CAGTATAAAT AACTAATGTC TCTACAATTT TGAAATAAAG CAACAGACTT 2322
 CTCAATAATC AATGAAGTAG CTGAGAAAAC TAAGTCAGAA AGTGCATTAA ACTGAATCAC 2382
 5 AATGTAAATA TTACACATCA AGCGATGAAA CTGGAAAAC TACAAGCCACG AATGAATGAA 2442
 TTAGGAAAGA AAAAAAGTAG GAAATGAATG ATCTTGGCTT TCCTATAAGA AATTTAGGGC 2502
 10 AGGGCACGGT GGCTCACGCC TGTAATTCCA GCACTTTGGG AGGCCGAGGC GGGCAGATCA 2562
 CGAGTTCAGG AGATCGAGAC CATCTTGGCC AACATGGTGA AACCTGTCT CTCCTAAAAA 2622
 TACAAAAATT AGCTGGATGT GGTGGCAGTG CCTGTAATCC CAGCTATTTG GGAGGCTGAG 2682
 15 GCAGGAGAAT CGCTTGAACC AGGGAGTCAG AGGTTTCAGT GAGCCAAGAT CGCACCCTG 2742
 CTCTCCAGCC TGGCGACAGA GGGAGACTCC ATCTCAAATT AAAAAAAA 2790

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 652 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Thr Pro Ile Leu Thr Val Leu Ile Cys Leu Gly Leu Ser Leu Gly
 1 5 10 15
 35 Pro Arg Thr His Val Gln Ala Gly His Leu Pro Lys Pro Thr Leu Trp
 20 25 30
 Ala Glu Pro Gly Ser Val Ile Thr Gln Gly Ser Pro Val Thr Leu Arg
 35 40 45
 40 Cys Gln Gly Gly Gln Glu Thr Gln Glu Tyr Arg Leu Tyr Arg Glu Lys
 50 55 60
 45 Lys Thr Ala Pro Trp Ile Thr Arg Ile Pro Gln Glu Leu Val Lys Lys
 65 70 75 80
 Gly Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr
 85 90 95
 50 Arg Cys Tyr Tyr Gly Ser Asp Thr Ala Gly Arg Ser Glu Ser Ser Asp
 100 105 110
 Pro Leu Glu Leu Val Val Thr Gly Ala Tyr Ile Lys Pro Thr Leu Ser
 115 120 125
 55 Ala Gln Pro Ser Pro Val Val Asn Ser Gly Gly Asn Val Thr Leu Gln
 130 135 140
 Cys Asp Ser Gln Val Ala Phe Asp Gly Phe Ile Leu Cys Lys Glu Gly

	145		150		155		160
	Glu Asp Glu His Pro Gln Cys Leu Asn Ser Gln Pro His Ala Arg Gly						
		165		170			175
5	Ser Ser Arg Ala Ile Phe Ser Val Gly Pro Val Ser Pro Ser Arg Arg						
		180		185			190
10	Trp Trp Tyr Arg Cys Tyr Ala Tyr Asp Ser Asn Ser Pro Tyr Glu Trp						
		195		200			205
	Ser Leu Pro Ser Asp Leu Leu Glu Leu Leu Val Leu Gly Val Ser Lys						
		210		215			220
15	Lys Pro Ser Leu Ser Val Gln Pro Gly Pro Ile Val Ala Pro Glu Glu						
		225		230			235
	Thr Leu Thr Leu Gln Cys Gly Ser Asp Ala Gly Tyr Asn Arg Phe Val						
		245		250			255
20	Leu Tyr Lys Asp Gly Glu Arg Asp Phe Leu Gln Leu Ala Gly Ala Gln						
		260		265			270
	Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser						
25		275		280			285
	Arg Ser Tyr Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser						
		290		295			300
30	Ser Glu Trp Ser Ala Pro Ser Asp Pro Leu Asp Ile Leu Ile Ala Gly						
		305		310			315
	Gln Phe Tyr Asp Arg Val Ser Leu Ser Val Gln Pro Gly Pro Thr Val						
		325		330			335
35	Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Gln Gly Trp Met						
		340		345			350
40	Gln Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala Asp Asp Pro Trp Arg						
		355		360			365
	Leu Arg Ser Thr Tyr Gln Ser Gln Lys Tyr Gln Ala Glu Phe Pro Met						
		370		375			380
45	Gly Pro Val Thr Ser Ala His Ala Gly Thr Tyr Arg Cys Tyr Gly Ser						
		385		390			395
	Gln Ser Ser Lys Pro Tyr Leu Leu Thr His Pro Ser Asp Pro Leu Glu						
		405		410			415
50	Leu Val Val Ser Gly Pro Ser Gly Gly Pro Ser Ser Pro Thr Thr Gly						
		420		425			430
55	Pro Thr Ser Thr Ser Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly						
		435		440			445
	Ser Asp Pro Gln Ser Gly Leu Gly Arg His Leu Gly Val Val Ile Gly						
		450		455			460

	Ile Leu Val Ala Val	Ile Leu Leu Leu Leu Leu Leu Leu Leu Phe	465	470	475	480
5	Leu Ile Leu Arg His Arg Arg Gln Gly Lys His Trp Thr Ser Thr Gln		485	490	495	
	Arg Lys Ala Asp Phe Gln His Pro Ala Gly Ala Val Gly Pro Glu Pro		500	505	510	
10	Thr Asp Arg Arg Leu Gln Trp Arg Ser Ser Pro Ala Ala Asp Ala Gln		515	520	525	
	Glu Glu Asn Leu Tyr Ala Ala Val Lys His Thr Gln Pro Glu Asp Gly		530	535	540	
15	Val Glu Met Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln Ala		545	550	555	560
	Val Thr Tyr Ala Glu Val Lys His Ser Arg Pro Arg Arg Glu Met Ala		565	570	575	
20	Ser Pro Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg		580	585	590	
	Gln Ala Glu Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu		595	600	605	
	Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg		610	615	620	
30	Arg Lys Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Pro Ser Pro Ala		625	630	635	640
	Val Pro Ser Ile Tyr Ala Thr Leu Ala Ile His *		645	650		
35						

WHAT IS CLAIMED IS:

1. A substantially pure or recombinant FDF03 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 2 or 4.
2. A substantially pure FDF03 polypeptide comprising the mature amino acid sequence set forth in SEQ ID NO: 2 or 4.
3. A substantially pure or recombinant YE01 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 6, 8, or 10.
4. A substantially pure YE01 polypeptide comprising the mature amino acid sequence set forth in SEQ ID NO: 6, 8 or 10.
5. A substantially pure or recombinant KTE03 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 12, 14, 16, 18, 20 or 22.
6. A substantially pure KTE03 polypeptide comprising the mature amino acid sequence set forth in SEQ ID NO: 12, 14, 16, 18, 20 or 22.
7. A fusion protein comprising the protein, peptide or polypeptide of any one of claims 1-6.
8. A binding compound which specifically binds to the protein, peptide or polypeptide of any one of claims 1-6.
9. The binding compound of claim 8 which is an antibody or antibody fragment.
10. A nucleic acid encoding the protein, peptide, or polypeptide of any one of claims 1-6.

11. An expression vector comprising the nucleic acid of claim 10.
12. A host cell comprising the vector of claim 11.
- 5 13. A process for recombinantly producing a polypeptide comprising culturing the host cell of claim 12 under conditions in which the polypeptide is expressed.

SUBSTITUTE SHEET (RULE 26)



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/21101		(74) Agents: MCLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).	
(22) International Filing Date: 5 December 1997 (05.12.97)			
(30) Priority Data: 60/032,252 6 December 1996 (06.12.96) US 08/762,187 9 December 1996 (09.12.96) US 60/033,181 16 December 1996 (16.12.96) US 60/041,279 21 March 1997 (21.03.97) US		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventors: ADEMA, Gosse, Jan; Haydnstraat 53, NL-6561 ED Groesbeek (NL). MEYAARD, Linde; Realengracht 68, NL-1013 KW Amsterdam (NL). GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US). MCCLANAHAN, Terrill, K.; 1081 Winchester Drive, Sunnyvale, CA 94087 (US). ZURAWSKI, Sandra, M.; 2005 School Road, San Juan Bautista, CA 95045 (US). ZURAWSKI, Gerard; 2005 School Road, San Juan Bautista, CA 95045 (US). LANIER, Lewis, L.; 1528 Frontero Avenue, Los Altos, CA 94024 (US). PHILLIPS, Joseph, H.; 15 Pine Avenue, San Carlos, CA 94070 (US).		(88) Date of publication of the international search report: 6 August 1998 (06.08.98)	
(54) Title: ISOLATED MAMMALIAN MONOCYTE CELL GENES; RELATED REAGENTS			
(57) Abstract Nucleic acids encoding various monocyte cell proteins from a primate, reagents related thereto, including specific antibodies, and purified proteins are described. Methods of using said reagents and related diagnostic kits are also provided.			

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/21101

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/13 C12N15/62 C12N15/63 C12N1/21 C07K14/705
C07K16/28 C12Q1/68 G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE : EMBL SEQUENCES EMBL, Heidelberg, FRG Accession No. H26010, 12 July 1995 HILLIER L ET AL.: "EST, Homo sapiens cDNA clone 161851" XP002061187 see the whole document ---	1
X	COLONNA M. & SAMARIDIS J.: "Cloning of immunoglobulin-superfamily members associated with HLA-C and HLA-B recognition by human Natural Killer Cells." SCIENCE, vol. 268, 21 April 1995, pages 405-408, XP002067321 Accession No. P43630 see figure 2 ---	3
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 June 1998

Date of mailing of the international search report

3 0. 06. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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Galli, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/21101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>DATABASE : EMBL SEQUENCES EMBL, Heidelberg, FRG Accession No. AA572674, 11 September 1997 STRAUSBERG R.: "EST, Homo sapiens cDNA clone IMAGE:914168" XP002061188 see the whole document</p> <p style="text-align: center;">---</p>	1,2
P,X	<p>MEYAARD L. ET AL.: "LAIR-1, a novel inhibitory receptor expressed on human mononuclear leukocytes" IMMUNITY, vol. 7, no. 2, 1997, pages 283-290, XP002061091 Accession No. AF013249 see abstract</p> <p style="text-align: center;">---</p>	3,4
P,X	<p>DATABASE GENBANK Accession No. U82279, 27 March 1997 SAMRIDIS J. & COLONNA M.: "Human immunoglobulin-like transcript 2 mRNA." XP002067322 & SAMARIDIS J. & COLONNA M.: "Cloning of novel immunoglobulin-superfamily receptors expressed on human myeloid and lymphoid cells." EUR. J. IMMUNOL., vol. 27, 1997, pages 660-665,</p> <p style="text-align: center;">---</p>	5,6
A	<p>PATENT ABSTRACTS OF JAPAN vol. 016, no. 501 (C-0996), 16 October 1992 & JP 04 187084 A (OTSUKA PHARMACEUT CO LTD), 3 July 1992, see abstract</p> <p style="text-align: center;">---</p>	1-13
A	<p>WO 95 29236 A (DANA FARBER CANCER INST INC) 2 November 1995</p> <p style="text-align: center;">---</p>	1-13
A	<p>US 5 314 992 A (GUYRE PAUL M ET AL) 24 May 1994 see abstract</p> <p style="text-align: center;">---</p>	1-13
A	<p>WO 96 34880 A (UNIV DUKE ;SQUIBB BRISTOL MYERS CO (US)) 7 November 1996 see abstract</p> <p style="text-align: center;">---</p>	1-13
A	<p>KORINEK V ET AL: "THE HUMAN LEUCOCYTE ANTIGEN CD48 (MEM-102) IS CLOSELY RELATED TO THE ACTIVATION MARKER BLAST-1" IMMUNOGENETICS, vol. 33, no. 2, 1 February 1991, pages 108-112, XP000566916</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-13

INTERNATIONAL SEARCH REPORT

International Application No

PCT/85 97/21101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JACKSON D.G. ET AL.: "Molecular cloning of a novel member of the immunoglobulin gene superfamily homologous to the polymeric immunoglobulin receptor" EUR. J. IMMUNOL., vol. 22, no. 5, 1992, pages 1157-1163, XP002061090 see abstract</p> <p>-----</p>	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/21101

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/21101

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1,2) - complete; (7-13) - partial

A purified monocytic protein, a purified fusion protein comprising it, binding compounds, antibodies.

DNA encoding said monocytic protein, vectors comprising said DNA, host cells harbouring said vectors. A process of producing recombinant protein by cultivation of said host cell.

Said proteins, DNAs, vectors and process, wherein the monocytic protein is FDF03 (Seq. ID 2 and 4)

2. Claims: (3,4) - complete; (7-13) - partial

Idem as subject matter 1, but limited to protein YE01 (Seq. ID 6,8,10)

3. Claims: (5,6) - complete; (7-13) - partial

Idem as subject matter 1, but limited to protein KTE03 (Seq. ID 12,14,16,18,20,22).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/21101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9529236 A	02-11-1995	US 5710262 A AU 2391195 A	20-01-1998 16-11-1995
US 5314992 A	24-05-1994	WO 9311222 A	10-06-1993
WO 9634880 A	07-11-1996	AU 5670396 A EP 0830373 A	21-11-1996 25-03-1998